SURGERY

VOL. 2 AUGUST, 1937 No. 2

Original Communications

HEPARIN AND THE THROMBOSIS OF VEINS FOLLOWING INJURY

D. W. G. MURRAY, M.D., L. B. JAQUES, M.A., T. S. PERRETT, M.D., AND C. H. BEST, M.D., TORONTO, CANADA

(From the Department of Surgery, Department of Physiology, and the School of Hygiene, University of Toronto)

WHILE it is well established that heparin increases the coagulation time of blood, little or no experimental work on the effect of this anticoagulant on the thrombosis of blood vessels resulting from injury to the intima has been carried out. It has been shown by Zahn,[1] Eberth and Schimmelbusch,[2] Welch,[3] and Zurhelle[4] that thrombosis of blood vessels may be produced by the application of caustics or by mechanical injury to the intima. These procedures result in the accumulation of blood platelets on the wall of the vessel at the point of injury. Leucocytes then collect at the margin of and between the platelet masses. Fibrin is subsequently laid down. Since the methods of producing the vascular obstruction used in the experiments to be reported here are essentially similar to those employed by these previous investigators, the mechanism by which obstruction is brought about is presumably the same. We have examined the blood vessels at short intervals after injury in only a few cases and cannot, therefore, describe in detail the sequence of events leading up to the formation of a plug which caused, in most of the control experiments, cessation of blood flow in the injured veins. Since in this investigation lesions in peripheral veins in which the blood flow is sluggish were being studied, it was to be expected that the obstructing mass would be composed, in large part, of red cells and fibrin. We are informed, however, by Professor Robinson, of the Department of Pathology, and by our colleague in the School of Hygiene, Dr. D. L. MacLean, that the plugs are typical thrombi. In

Received for publication, March 8, 1937.

some sections, accumulations of platelets are clearly visible, while in others the manner in which the formed elements are laid down distinguishes the obstructing mass from a clot.

In this study, injury to the lining of the veins was produced by two procedures. The first was mechanical and the second chemical. When a solution of purified heparin was administered intravenously for an adequate period, the incidence of obstruction by thrombus was very definitely less than in the experiments in which the anticoagulant was not used.

METHODS

Normal healthy dogs, weighing from ten to fifteen kilograms, have been used as experimental animals. Ether or nembutal has been

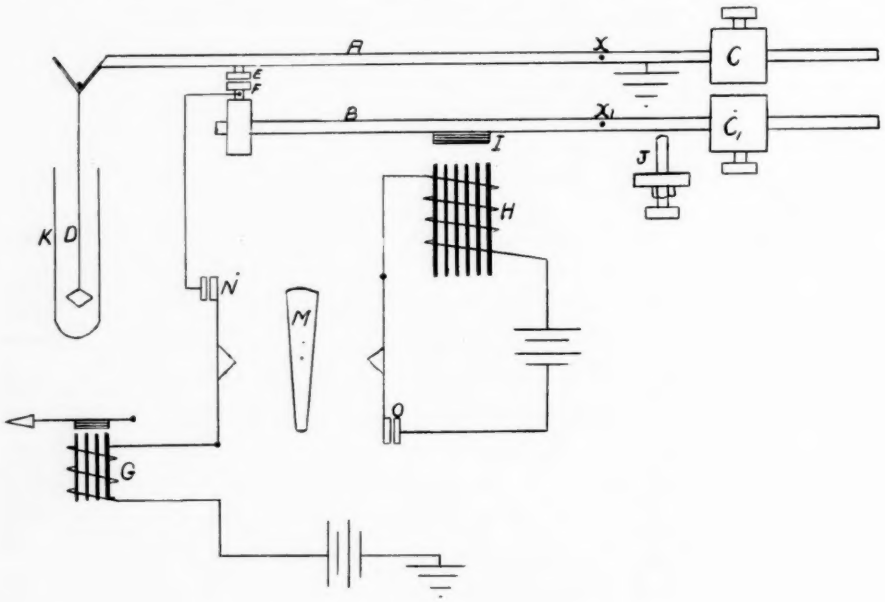

Fig. 1.

employed when anesthesia was necessary. In the determination of the coagulation time of the blood such great variation was found that considerable effort was made to secure a method which would give a consistent end-point. The difficulties of securing uniform results may be divided into two groups; first, those associated with the removal of the blood from the veins, and second, those involved in the subsequent care and handling of the sample. In confirmation of the results of previous investigators, it was found impossible to take repeated samples of blood, using a syringe and needle, from the same part of the vein without shortening the coagulation time very appreciably. The third and fourth samples would often gel before they could be placed in the recording apparatus. The same difficulty was encountered in obtaining samples from cannulas or from a sectioned artery.

The differences in coagulation time are no doubt due to the release of clotting factors from the traumatized areas. These difficulties can be eliminated, to a certain extent, by drawing the blood with a very small needle if certain precautions are used. The point of the needle is directed against the flow and is inserted some distance into the blood vessel. Each subsequent sample is secured from a slightly more peripheral point on the vessel. Care must be taken that the blood flows easily into the syringe and that no air enters during the withdrawal of the plunger. Even when attention is paid to these details, variations in the clotting time occur. If they are neglected, little significance can be attached to the end-point which is secured. The subsequent handling of the blood samples presents less difficulty. After testing most of the methods which have been advocated, we decided to use a mechanical device which eliminates subjective factors. The principle of our coagulometer is similar to that developed by Cannon and Mendenhall[5] and modified by Stoker.[6]

Coagulometer.—Two metal levers, *A* and *B*, are mounted on pinpoint bearings at *X* and X_1. *A* is parallel to, and about 2 cm. above, *B*. At one end of each lever, weights *C* and C_1 are attached. These may be finely adjusted and locked at any point. At the opposite end of *A* is a fork which supports, between its arms, the plunger *D* (weight, 1.340 gm.). This plunger is constructed from monel metal and in shape resembles two shallow cones placed base to base. The diameter at the largest point is 8 mm. Into a hole bored through the apices is soldered a short length of monel wire. To the other end of the wire a cross-piece, to serve as a means of support when the plunger is suspended from the fork, is attached.

Between the fork and the fulcrum is attached a platinum point *E* which makes contact with a similar point *F* on the lever *B*. *F* is insulated from the lever *B*. These points are connected in series with the signal magnet *G*.

Under *B* is mounted an electromagnet *H* which, when charged, pulls down the lever *B* by means of the soft iron armature attached at *I*. When the circuit is broken, the lever will return to the horizontal because of the extra weight of C_1. An adjusting screw at *J* controls the extent of this movement. As the weight of *A* is greater at the forked end, the points *E* and *F* will be held in close contact and the movements of *B* transmitted to *A* through these points.

The weight *C*, on *A*, is adjusted so that the lever will just remain horizontal when *D* is replaced by a standard weight of 1.000 gm.

In operation, 1 c.c. of blood is placed in the test tube *K* (10 mm. bore by 50 mm. high) and the height of the test tube adjusted so that the plunger is just clear of the bottom when the levers are held down against *H*. At intervals of one minute and for a period of three seconds the magnet *H* is stimulated. This pulls down the lever *B* and permits the plunger *D* to sink, by its own weight, in the blood. If the blood is not coagulated, contact is made at the points *E* and *F* and the signal magnet *G* will record this on a kymograph. If the blood is coagulated, the plunger will be supported by the clot and no contact will be made. A record in one-minute intervals is recorded on the kymograph. This record ceases when the blood is clotted.

An ordinary household electric clock is used to control the make-and-break mechanism for the electromagnets. The second hand is replaced by a tapered arm *M* which once in every revolution closes the contacts *N* and *O*. The wide end of the

lever *M* holds the points *O* in contact for three seconds while the narrow end closes the points *N* for one second. Contact at *N* should synchronize with the third second of contact at *O*. If contact is made earlier or later, a misleading record may be made. The contact points *N* and *O* should be mounted on the clock face, one a little in front of the other, and the lever *M* attached slightly off the right angle. If mounted in the same plane, contacts would be made at thirty-second intervals.

The apparatus in use is composed of four of the above units. One electric clock is sufficient to operate all four. The levers *B* are secured firmly to a shaft carried by two end-bearings. This shaft has attached to it an extra lever, carrying a weight at one end and an armature, similar to that shown on *B*, at the other. The weight is sufficiently heavy to balance all the levers. By this means the four units are operated by one magnet.

In an endeavor to obtain accurate checks on the blood contained in the four tubes and filled from the same sample, the test tubes are partially immersed in a constant temperature water-bath which is kept at 37° C. The tubes are held in place by spring clamps attached to one side of the bath.

The weights of the plungers are adjusted to within 2 mg., and as the levers are balanced to the standard weight of 1.000 gm., the downward pressure exerted by any plunger is equivalent to 0.340 gm. (weight of *D* [1.340 gm.] - 1.000 gm.).

Method of Producing the Injury to Veins.—A. Mechanical means: The blood vessels chosen for these experiments were the readily accessible radial and saphenous veins. Very little dissection was needed to free them from the surrounding tissue. The skin incision was made at some little distance to the side of the vein and the skin undercut so that, when sewing up, the flap would fall over the vein. After about one inch of the vessel had been isolated in this way, a needle carrying a length of silk thread (size 000) was passed up through the lumen of the veins for about three-quarters of an inch so that the thread remained within the vessel wall. The vein was then crushed against the thread between the jaws of a pair of artery forceps. The forceps were clamped very tightly on the vein. The crushing was continued along the full length of the exposed vein and then repeated in at least two other planes. In later experiments, a pair of forceps with a particularly firm grip was selected and used only for the purpose of crushing. After the injury the thread was withdrawn, bleeding controlled with gauze, and the wound closed by interrupted silk sutures. The veins were left in situ for periods ranging from seven hours to seven days. They were then removed between ligatures, examined in the gross, and placed in formalin as the first stage in their preparation for microscopic examination.

B. Injury produced by injection of sodium ricinoleate (soricin): The second method of producing occlusion of the veins was by the injection of a solution of sodium ricinoleate. This was a commercial preparation manufactured by the Wm. S. Merrell Company, Cincinnati, U. S. A. The needle of the syringe containing the soricin is introduced through the skin into the vein. The vein is then occluded one or one and one-half inches above the needle by pressure with the

finger. It is obvious that great care must be taken to use the same length of vein in all the experiments of one series. Unhappily, the calibers of the veins cannot readily be measured and must be assumed to be equal. If the volumes of blood in the occluded veins are not similar, the concentrations of soricin to which the intimal surfaces are exposed will vary. If branches of the veins can be detected, these are also occluded by pressure. The sodium ricinoleate solution is then injected and prevented from escaping from the vein by pressure over the point at which the needle entered. The solution is kept in this manner in the vein for a period of three minutes. The vein is then released.

Method of Administering Heparin.—In the preliminary stages of this investigation heparin was administered in a variety of ways. Certain descriptive terms have come into use in these laboratories. Local heparinization is the term used to describe the application of heparin to one particular area. This procedure was used in experiments on blood vessel surgery. Heparin was incorporated in vaseline or jelly and applied to the edges of the blood vessels about to be sutured. No significant result has been obtained by this method of administering the anticoagulant. Regional heparinization is the term used to describe the administration of heparin in such a way that the coagulation time of the blood of one limb, for example, is increased without materially affecting the blood in other parts of the body. Thus, with an infusion of heparin into the femoral artery of one limb, blood samples from the veins of the same leg show a longer clotting time than those secured at the same time from other parts of the body. This is true, however, only when small doses of heparin are administered. With larger doses more of the anticoagulant reaches the general circulation and the increase in clotting time is general. The term general heparinization describes the results of the administration of heparin into a vein or artery at such a rate that the clotting time of the blood from all parts of the body is increased. Most of the results which we are reporting in this paper were secured by general heparinization of experimental animals. The heparin was given intravenously by one of three methods. In preliminary experiments, a single injection was made by syringe. In a second series, a continuous injection of heparin dissolved in saline was made by means of a motor-driven pump. Animals receiving the anticoagulant by this procedure were maintained under nembutal anesthesia and the injection was continued for, at most, ten hours. The third method was by a continuous injection of heparin in saline, utilizing, with slight modifications, the technique adopted by Jacobs,[7] of Chicago. By this procedure it is possible to give continuous intravenous infusions to dogs for long periods of time without seriously interfering with their activity. Ether anesthesia was used during the insertion of a cannula

into the external jugular vein. The cannula was connected by a flexible metal tube to a reservoir containing the heparin solution. After recovery from the anesthetic, the animal moved about with considerable freedom. The rate of injection was maintained at a constant level by a motor-driven pump. The injections by this method were usually continued for seventy-two hours. The parts of the apparatus which it was not feasible to sterilize by heat were thoroughly bathed with antiseptic solution before each experiment.

THE TOXICITY OF HEPARIN

Since it was our hope that heparin might ultimately be safely used in human patients, the toxicity of the various preparations of this anticoagulant was a very important matter. It is evident from the literature and from our own findings that the toxicity varies greatly and, in general, inversely as the purity of the preparation.

The Howell unit of heparin is the amount which will prevent the clotting of 1 c.c. of cat's blood for twenty-four hours. Even when precautions are taken with regard to temperature, stirring, etc., it is impossible to estimate the potency of the solution accurately by this procedure without the use of a standard preparation. However, if a standard heparin is used and the unknown preparation compared with this, reliable results may be obtained. A standard of heparin has been set up in the Connaught Laboratories and the heparin which we have used has always been compared with this preparation.

Using heparin of a potency of 15 units per milligram, Howell and McDonald[8] injected an amount into a dog which was sufficient to render its blood incoagulable. This was approximately 0.45 mg. per kilogram. This injection was repeated daily for five days. They reported no demonstrable change in the red and white blood counts or in the platelets. There was no indication of any deleterious effect on the animal. Reed[9] injected moderate quantities of heparin intravenously in normal and etherized dogs and rabbits. He found no change in temperature, no cardiovascular effect, no concentration of the blood cells, and no abnormalities in respiration. In 1924, Mason[10] reported on the use of material containing 5 units per milligram. He added from 50 to 300 mg. to blood used in transfusing human patients. In about one-half the cases he observed reactions which varied from slight chills to severe headache, high fever, and nausea. Mason concluded that while the heparin used in the early part of his work was too toxic to warrant its routine clinical use in doses of 100 mg. (500 units), preparations subsequently made had given encouraging results. Howell[11] reported upon the use of heparin containing 100 units per milligram in transfusions given to human subjects. He reported a slight reaction in two of the ten transfusions carried out on six patients. Godlowski[12] found no evidence of toxicity in his pa-

tients when he injected 1 mg. of heparin per 10 c.c. of blood. This preparation contained 10 units per milligram. In our experience, the 5 unit material, which was the only preparation readily available when these experiments were started, exerted marked toxic effects when administered intravenously to dogs. Some of these dogs died and at autopsy revealed marked hemorrhages in the intestine. Later, using more highly purified heparin, 75 units per milligram, no deaths were produced in a series of some twenty dogs studied. Vomiting and pronounced muscular weakness were, however, not infrequently observed when large doses of the material were used. Recently we have employed more highly purified heparin and in some sixty dogs which received a preparation with a potency of about 250 units per milligram, for a period of seventy-two hours (500 mg.; i.e., 125,000 units of heparin in all were injected), no signs of a toxic action of the anticoagulant were detected.*

Tests for the toxicity of this heparin containing 250 units per milligram were made upon various species of animals. Rabbits, guinea pigs, and mice were injected with sufficient of the material to render their blood incoagulable for very long periods of time. No toxic effects were produced. These findings have, however, relatively little significance in view of the fact that heparin has been much further purified by our colleagues Charles and Scott since the studies of toxicity referred to above were carried out. More recently we have had available adequate amounts of heparin of a potency of 500 units per milligram. This is dissolved in distilled water or saline and 1 c.c. of this solution usually contains approximately 15,000 units of the anticoagulant. The effect on human subjects will be described in more detail later, but it may be stated here that the 250-unit heparin produced definite signs of toxicity. More highly purified material, however, has been given to patients with no deleterious effects. Since adequate amounts of this relatively innocuous and very potent material are now available, it is unnecessary to describe in detail the results of toxicity tests on the cruder preparations.

EXPERIMENTAL RESULTS AND COMMENTS

Injury Produced by Mechanical Means.—When the veins of a dog are crushed upon a thread inserted in the lumen, as described under Methods, thrombosis will take place in only a limited number of the veins unless considerable force is applied in the crushing process. If force is exerted and extensive damage to the veins produced, a thrombus will form, according to our experience, in approximately 80 per cent of the cases (Table I). If this thrombus is left in situ for five or six days it is usually found, upon removal of the veins, that it entirely fills the lumen and is adherent to the vein wall. The

*We are indebted to Miss Winifred Chute for help in some of the early experiments.

incidence of obstruction by thrombus formation in a vein which has been injured, as described above, is extremely small as long as the animal is maintained under the influence of heparin. An experiment of this nature was conducted in which thirteen veins were observed. Following a single injection of heparin the veins were damaged, but they were removed before the effect of the heparin had worn off. All the veins of this group except three were perfectly clear on macroscopic examination. In these three, a small thrombus was present on a portion of the wall. Without heparin the veins (i.e., 80 per cent of them) are found to be obstructed by thrombus when examined forty minutes after injury.

TABLE I

METHOD OF INJURY	NO. OF VEINS	PATENT	OCCLUDED	PARTIALLY OCCLUDED	PER CENT OCCLUDED
Crushing—moderate, no thread used	10	9	1	0	10
Crushing—moderate, thread used	10	6	4	0	40
Crushing—severe, thread used	57	8	44	5	80

It was found that an adequate effect was produced upon the coagulation time of blood in dogs; i.e., the coagulation time was maintained at approximately thirty minutes, when relatively crude heparin was administered intravenously at the rate of 3.3 units per kilogram per minute. In the next experiment to be described, heparin was given intravenously in saline solution at this rate. The veins were traumatized and the injection continued for seventy hours. At the end of this time the veins were excised and examined. Four veins of one dog were used in this experiment. They were all perfectly clear and no trace of thrombus could be found. Further details of these experiments and of the results obtained are given in Table II.

TABLE II

NO. OF VEINS	HEPARIN MG./KG.	CALCULATED HEPARIN EFFECT	VEINS LEFT IN SITU	PATENT	OCCLUDED	PARTIALLY OCCLUDED
13 (5)	60*	1½ hr.	1 hr.	5	0	
13 (6)	140*	3½ hr.	3 hr.	6	0	2 (very small thrombus)
13 (2)	180*	4½ hr.	4 hr.	2	0	1 (very small thrombus)
4	0.22 mg./kg./min.	70 hr.	70 hr.	4	0	

*Single injection.

In the next series of experiments, thirteen veins were studied in animals which had received a single injection of heparin. The vein was traumatized immediately after the injection of heparin had been made but was left in situ for periods of from three and one-half to

twenty-four hours. The amount of heparin injected varied in the different experiments. The results of this series are given in Table III. It will be noted that of the thirteen veins one was partly occluded while the remaining twelve were completely filled with thrombus and clot.

TABLE III

NO. OF VEINS	HEPARIN MG./KG.	CALCULATED HEPARIN EFFECT	VEINS LEFT IN SITU	PATENT	OCCLUDED	PARTIALLY OCCLUDED
1	60	1½ hr.	3½ hr.	0	0	1
8	100	2½ hr.	4½ hr.	0	8	0
4	180	4½ hr.	24 hr.	0	4	0

In the next series of experiments single injections of heparin (approximately 6,000 units) were given to 10-kilogram dogs. The veins were then damaged and an infusion of heparin in saline solution started immediately. This was maintained at a rate of 2.2 units per kilogram per minute for from seventy to seventy-two hours. The veins were inspected seven days after they had been injured. Nine veins were treated in this manner. Six of these showed clear lumina and a smooth, glistening intima. Three were occluded by thrombi. In one of these the obstruction was at the site of a valve to which the thrombus was attached. In the other two cases the veins were exposed for some time on the surface of an infected wound (Table IV).

TABLE IV

NO. OF VEINS	HEPARIN GIVEN	EXAMINED	PATENT	OCCLUDED	PARTIALLY OCCLUDED
9	72 hr.	7 days after injury	6	3*	0

*One thrombus attached to valve curtain: 2 veins exposed on surface of infected wound.

In the next group of experiments a vein on one side of an animal was traumatized, but no heparin was administered. This vein was examined seven to twenty-four hours later and if obstructed the corresponding vein on the other side of the animal was similarly traumatized after the injection of heparin had been started. In this group of experiments with ten control veins and ten under test, one of the controls was only partially occluded while one of the veins which had been bathed with heparin became completely plugged by thrombus. There is, perhaps, an explanation for this latter case in that the pump which was forcing the heparin into the animal stopped and the full dose of the anticoagulant was not received (Table V).

In the next series 28 veins were studied. The procedure was the same as in the preceding experiment, with one exception. The control veins, i.e., those which were not bathed by heparin, instead of being examined in 7 to 24 hours, were left in situ for 7 days. Heparin

TABLE V

RIGHT VEINS (CONTROLS)—EXAMINED AND EXCISED IN 7 TO 24 HOURS
LEFT VEINS (HEPARIN)—HEPARIN 72 HOURS—EXAMINED 7 DAYS AFTER INJURY

RIGHT VEINS (NO HEPARIN)					LEFT VEINS (HEPARIN GIVEN)					
NO. OF VEINS	EXAMINED	PATENT	OCCLUDED	PARTIALLY OCCLUDED	NO. OF VEINS	HEPARIN GIVEN	EXAMINED	PATENT	OCCLUDED	PARTIALLY OCCLUDED
10	7-24 hr.	0	9	1	10	70 hr.	7 days	9	1*	0

*The pump stopped overnight and the full amount of heparin was not received.

was administered for a period of 70 hours and the test veins were left in place for 6 days after the traumatization. The results of these series are shown in Table VI.

TABLE VI

RIGHT VEINS (CONTROLS)					LEFT VEINS (HEPARIN GIVEN)					
NO. OF VEINS	EXAMINED	PATENT	OCCLUDED	PARTIALLY OCCLUDED	NO. OF VEINS	HEPARIN GIVEN	EXAMINED	PATENT	OCCLUDED	PARTIALLY OCCLUDED
14	7 days	4	8	2	14	70 hr.	6 days	11	3*	0

*In 2 of these cases there was an extensive hematoma.

While it is very difficult to summarize the results of these experiments in which injury to the veins had been produced by mechanical means, this is attempted in Table VII. When no heparin was given,

TABLE VII

NO HEPARIN					HEPARIN					
NO. OF VEINS	EXAMINED	PATENT	OCCLUDED	PARTIALLY OCCLUDED	NO. OF VEINS	HEPARIN GIVEN	EXAMINED	PATENT	OCCLUDED	PARTIALLY OCCLUDED
10	7-24 hr.	0	9	1	4	70 hr.	70 hr.	4	0	0
14	7 days	4	8	2	9	70 hr.	7 days	6	3	0
33	7 hr.-7 days*	4	27	2	10	70 hr.	7 days	9	1	0
					14	70 hr.	7 days	11	3	0
Totals 57		8	44	5	37			30	7	0

*Four of these veins were removed and examined after 7 hr.; 9 after 24 hr.; 8 after 48 hr.; 4 after 5 days; and 8 after 7 days.

8 of the 57 veins examined were, macroscopically, free of thrombus. (The 33 veins of the control series in this table were referred to in Table I. They were included in the group consisting of 57 veins.)

Of 37 cases in which heparin was administered to the animals, 30 of the 37 veins were free of thrombus as judged by macroscopic examination. The figures are taken from all the experiments in which heparin was administered for prolonged periods.

Injury Produced by Chemical Means.—The procedure used in damaging the intima of the veins by chemical means has been described under Methods. After some preliminary experiments had been carried out, we studied the effects of heparin on injury produced when 0.25 c.c. of soricin was injected into each vein. Some 204 veins were studied in this series. No useful purpose will be served by describing the experiments in great detail. The results are summarized in Table VIII. It will be observed that of the 114 veins from animals which

TABLE VIII

	CONTROLS			HEPARIN				
NO. OF VEINS	OCCLUDED	PATENT	PER CENT OCCLUDED	OCCLUDED	PATENT	PER CENT OCCLUDED	HEPARIN U./KG./HR.	HEPARIN GIVEN
204	97	17	85	44	46	47	22.5	66-72 hours

0.25 c.c. soricin injected in all veins. Controls, 15 per cent patent; heparin, 53 per cent patent.

received no heparin, 85 per cent were occluded. Of the 90 veins investigated from animals which received heparin, 47 per cent were occluded. In other words, 15 per cent of the control veins were patent while 53 per cent of those which had received heparin were open after from 4 to 7 days. The obvious deduction from the results of this large series of experiments is that heparin in the dose used, i.e., 22.5 units per kilogram per hour, is not nearly so effective as might be desired in preventing thrombosis of veins. While a dose of 0.25 c.c. of soricin, under the conditions which we have described, does not produce occlusion in all cases, it was thought expedient to determine whether smaller doses might not be nearly as effective. An injection of 0.15 c.c. of soricin was tried in a series of 24 veins. The results in Table IX show that in 83 per cent of the control series the

TABLE IX

	CONTROLS			HEPARIN				
NO. OF VEINS	OCCLUDED	PATENT	PER CENT OCCLUDED	OCCLUDED	PATENT	PER CENT OCCLUDED	HEPARIN U./KG./HR.	HEPARIN GIVEN
24	10	2	83	0*	12	0	22.5	68-73 hours

*A very small thrombus which produced no obstruction of blood flow was found in one vein.

0.15 c.c. soricin injected in all veins. Controls, 17 per cent patent; heparin, 100 per cent patent.

veins were occluded by thrombi. When heparin was given in the dose which was used in most of the previous experiments, 11 of the 12 veins were completely free of thrombus. In 1 vein, while there was no interference with blood flow through it, there was a small thrombus firmly attached to the wall. Interestingly enough, this thrombus was composed almost entirely of platelets. These results appear to show that if a small dose of soricin is used, its effect, so far as the obstruction of veins is concerned, may be almost completely counteracted by an adequate dose of heparin administered continuously for a period of approximately 70 hours.

It may be noted here that if the veins are examined before the injection of heparin is discontinued, thrombosis is not observed in most cases even when much larger doses of soricin are used (up to 1.0 c.c.). Under these circumstances, thrombosis would presumably have occurred invariably soon after the effect of heparin had worn off. These higher concentrations of soricin produce almost complete destruction of the tissue with which they come in contact. Our findings also suggest that the animals should always be thoroughly heparinized before the injury to the veins is produced, if the action of the anticoagulant in preventing obstruction is to be most effective.

Regional Heparinization in Experimental Animals.—A large number of experiments in which attempts have been made to heparinize one limb of an experimental animal without affecting the blood in other parts of the body have been carried out. It will be sufficient for our present purpose to describe one experiment in some detail.

A dog weighing approximately 7 kg. was anesthetized by an intravenous injection of nembutal. Both femoral arteries and veins were exposed. The clotting time of the blood from the vein of the right leg was 5 minutes, and of that from the left leg, 4 minutes. Heparin solution was then introduced from a buret through a needle into the right femoral artery. The solution contained approximately 2,200 units per cubic centimeter. Ten minutes after the injection had been started, the clotting time of the blood secured from the vein of the neparinized limb was 11 minutes, while that from the unheparinized extremity was 5 minutes. Thirty-five minutes after the start of injection, blood from the right femoral vein showed a clotting time of 11 minutes, while 15 minutes later blood secured from the unheparinized left limb showed a clotting time of 6 minutes. The heparin solution was injected at the rate of approximately 0.7 c.c. per minute. Four hours and thirty minutes after the start of the injection the clotting time on the heparinized side was 21 minutes, while on the other side the time was 20 minutes. The results of this experiment show that regional heparinization can be accomplished, for a time at least, when an injection of heparin solution is made intraarterially at a fairly slow rate. After some time, however, in many of the experi-

ments the clotting time of blood from other parts of the body showed the effects of heparin; i.e., the heparinization had become general. It is possible, of course, that if the rate of injection had been decreased regional heparinization might have been maintained.

Observations on Human Subjects.—While a more detailed report will be made later on the results of the use of heparin in human subjects, a summary of the findings we have secured will be included here. The objective in these investigations was merely to determine the toxicity of the heparin preparations on human subjects and the effect on the clotting time of the blood.

The first administration of heparin to a patient on the surgical ward of the Toronto General Hospital was carried out on April 16, 1935. The brachial artery of the left arm was exposed by a small incision under local anesthesia. A needle was inserted in the artery and the heparin solution was injected by means of a motor-driven pump. To make this solution, heparin powder with a potency of approximately 250 units per milligram was dissolved in saline solution and the mixture sterilized by passage through a Berkefeld filter. Samples of blood from the veins of the injected arm showed a rise in clotting time from the normal of 6 minutes to a value approximately 18 minutes. Samples of blood from other parts of the body showed, at this time, no change in clotting time. This is an example of regional heparinization in a human subject. The injection was maintained for a period of approximately 4 hours and no signs of any toxic effects were observed. Regional heparinization was carried out in several other cases.

No evidence has been obtained in experimental animals or human subjects that a negative phase, i.e., a decrease in coagulation time, develops when the injection of heparin is discontinued.

The general heparinization of the human subject was attempted on several occasions with relatively crude heparin. Toxic effects in the form of weakness, headache, and slight chills made it inadvisable to continue the injections. More recently, using heparin of a potency of 250 units per milligram, 4 of 9 clinical cases showed no toxic effects even after prolonged injection. The other 5 of these cases, however, did exhibit definite signs of toxicity and the injections of heparin had to be discontinued. The effect of a single large dose of this preparation of the anticoagulant (22,000 units) rapidly administered to a patient is illustrated in Fig. 2. This patient was receiving heparin continuously at a slow rate and had been given an injection of 11,000 units one hour and ten minutes before the larger amount was administered. The rise in blood clotting time after the last injection may have been due, in part, to the effects of the previous dose.

More recently large amounts of highly purified heparin, 500 units per milligram, have been available. In the course of the purification

of this substance, Charles and Scott were able to remove rather large quantities of a tarlike material which it is believed may have been responsible for the toxic properties of the cruder preparations. Seventy-six postoperative cases have now received injections of the

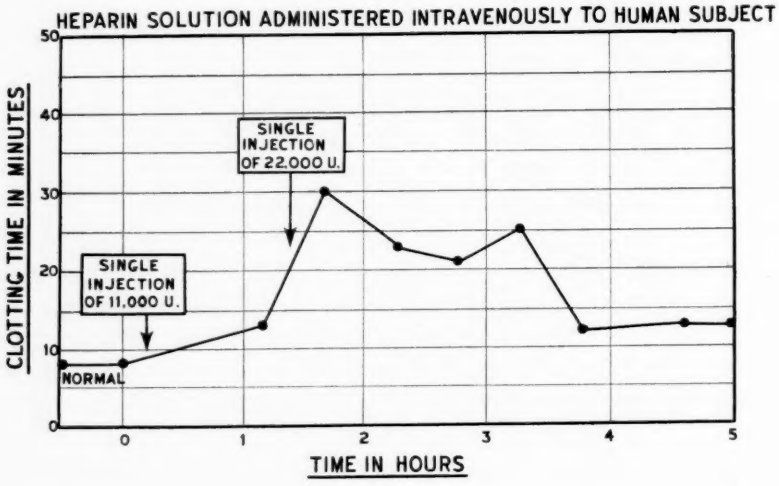

Fig. 2.

solutions of purified heparin by the intravenous route. The period of injection has usually varied from 24 to 120 hours. An effort has been made to keep the clotting time at approximately 15 to 20 minutes, i.e., at least two or three times the usual normal range, but very

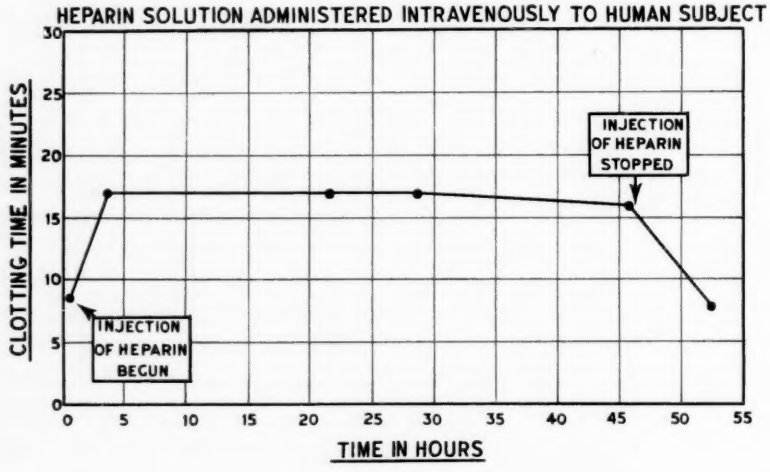

Fig. 3.

high values (51 minutes) have sometimes been observed. The results on one of these cases are illustrated in Fig. 3. The findings in this case are more regular than in some of the others and it has been chosen for this reason. In other cases the clotting time was fre-

quently raised to a much higher level but, as stated above, no deleterious effects were observed. The cases which received heparin postoperatively had undergone one of the following operations: appendectomy, herniotomy—with and without living sutures—resection of colon, closure of colostomy, partial gastrectomy, drainage of empyema, bone graft of the tibia and of carpal scaphoid, or various minor operations such as excision of cysts, lipomata, and so on. In only one of these cases was there a hematoma at the site of operation. This was in the skin and while it may be attributed to heparin, it is also possible that it was due to inadequate hemostasis. The injections of heparin were commenced in from 2 to 3 hours after the completion of the operation.*

Histologic Findings.—The histologic picture of veins thrombosed as a result of mechanical injury has been described by previous investigators. Our findings recorded in the tables are based on gross examination. Histologic sections were prepared of all the veins and the findings support, in general, those of the gross examination. In some cases platelet thrombi were found under the microscope in veins which had been considered on gross examination to be perfectly clear. Many of the heparinized veins, however, appeared to be completely free of thrombi, but in some of these inflammatory areas of varying sizes were present in the media or adventitia. These findings are based on examinations of several sections, but serial sections were not made.

The veins into which soricin had been injected and which subsequently became obstructed contained, on histologic examination, a mixed thrombus. If this examination was conducted twenty-four hours after the injection of the irritant, the veins were found to exhibit loss of endothelium from part of the wall and substitution of this by a line of fine dark-staining granular matter. This was probably a mixture of disintegrated nuclei and soricin. The media of these veins showed varying degrees of degeneration. In some cases a large area of this layer failed to take the nuclear stains. In other cases the nuclei and fibers stained well. The former were pyknotic and broken into fine granules. The muscle fibers were separated by widely dilated capillaries and in some cases by interstitial hemorrhage. The adventitia showed changes in some cases and not in others. If any of the irritant material which was injected had leaked out of the vein, there was a marked inflammatory reaction. The thrombus examined at this stage usually filled the entire lumen and was attached over a fairly large area of the vein wall by platelets and a network of fibrin in which red and white cells were visible.

*A report of the earlier part of this work was presented before the Junior Inter-Urban Surgical Club of Canada in October, 1935.

The site of injection sometimes involved a valve area and in these cases the thrombus was often found attached to one of the valve leaflets.

Fig. 4.—Photomicrograph of vein showing complete thrombosis. 0.25 c.c. soricin, excised after seventy-two hours. (H. and E. stain ×75.)

Fig. 5.—Section of same vein as shown in Fig. 4. (H. and E. stain ×750.)

In 72 hours after the injection, the media usually took a nuclear stain. The nuclei, however, were broken and disintegrated and the

spaces between the muscle fibers were filled with phagocytic cells containing dark-staining granules and red cells. The thrombus filling

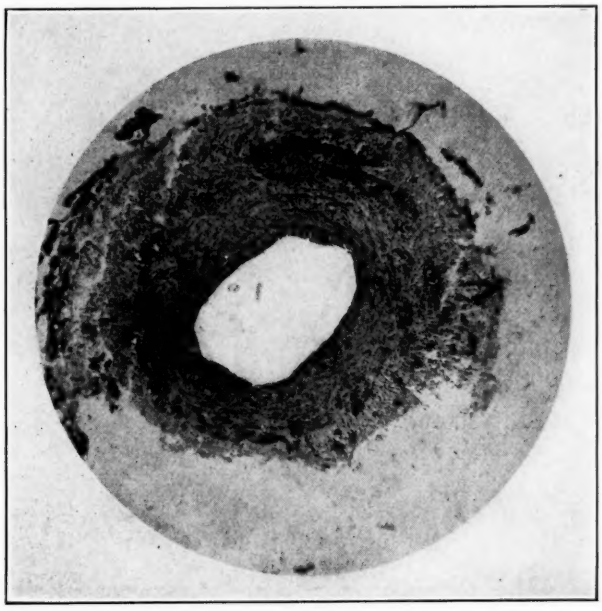

Fig. 6.—Photomicrograph of vein showing no thrombosis. 0.25 c.c. soricin, heparin sixty-five and a half hours, excised on seventh day. (H. and E. stain ×75.)

Fig. 7.—Section of same vein as shown in Fig. 6. (H. and E. stain ×375.)

the lumen appeared to be attached directly to the media in some places from which heavy fibrin threads extended outward. These

were usually covered with platelets and white cells. This gave the thrombus a wavy, lacy appearance.

Fig. 8.—Photomicrograph of vein showing very small thrombus. 0.25 c.c. soricin, excised after twenty-four hours. (H. and E. stain ×100.)

Fig. 9.—Photomicrograph of vein showing partial thrombosis. 0.15 c.c. soricin, heparin seventy-three hours, excised on seventh day. (H. and E. stain ×45.)

In the heparinized veins, sections secured 60 to 72 hours after the injection of soricin showed, in those cases where there was no obstruc-

tion to blood flow, a complete freedom from thrombus formation in many instances. In others a small thrombus attached to a valve or

Fig. 10.—Section of same vein as shown in Fig. 9. (H. and E. stain ×375.)

Fig. 11.—Photomicrograph of vein showing organization of a thrombus. 0.25 c.c. soricin, vein removed seventh day after injury. (H. and E. stain ×375.)

to a tiny area on the vein wall was visible under the microscope. The vessel wall, even when no thrombus was seen, showed in some areas

signs of inflammatory reaction. The intima was usually normal although the nuclei seemed to be enlarged. The media usually showed an engorgement of capillaries and hemorrhage between the fibers. The nuclei of the cells of the media appeared broken or pyknotic. White blood cells were present in this layer and these were filled with dark-staining granules. The adventitia in a few cases showed signs of inflammatory reaction. The above findings were secured when the veins were removed 3 days after the injury. Six or 7 days after injury the vessel walls seemed to be largely free of inflammation but the cells of the intima were still rather hyperchromatic.

In the veins where a thrombus had formed there were definite signs of organization at the end of 6 days. The above points are illustrated in Figs. 4 to 11 inclusive.

DISCUSSION

The possibility that heparin might prevent thrombosis of blood vessels was appreciated by Howell and by many of the subsequent workers in this field. It has been shown by Mason[13] that heparin will prevent the intravascular clot produced by the injection of a potent solution of thrombokinase into the blood stream. Our investigations have differed from those which have preceded them in the following ways: (1) Thrombosis of veins was produced by mechanical and chemical injury to the intimal surface of the blood vessels. (2) In our more recent experiments a very highly potent and nontoxic preparation of heparin has been available in adequate quantities.

It has not previously been shown, to our knowledge, that heparin is capable of preventing the obstruction of blood vessels by thrombus and clot which form as a result of extensive injury. To accomplish this it is necessary, as we have shown, to keep the animal under the influence of heparin for prolonged periods. The heparin which was available when Mason conducted his very interesting experiments on the prevention of intravascular clotting by thrombokinase presumably had a potency of approximately 5 units per milligram. Some of our work has been conducted with heparin of a potency of 250 units per milligram, while more recently this has been of the order of 500 units per milligram. It is necessary to secure a high degree of purification if toxic products are to be eliminated. The administration of heparin of a potency of 250 units per milligram, in amounts effective in increasing the clotting time of the blood, for prolonged periods to human subjects is not a feasible procedure.

It should be appreciated that considerable care is required in conducting experiments in which the occlusion of veins is produced by mechanical injury. It is probable that if the veins of animals which were to receive heparin had been less severely injured than the controls, a large proportion of them would have failed to become occluded.

In our opinion, the heparinized veins were damaged quite as severely as the controls. If there was any difference in the extent of injury, we believe that the heparinized veins received the more severe traumatization.

There would seem to be less possibility of significant variation in the procedure used to injure the veins by chemical means. The soricin was injected under rigidly uniform conditions. While it is very interesting that the heparin was not effective in preventing occlusion of a larger proportion of the veins into which 0.25 c.c. of the soricin was injected, it would appear that there is a very significant difference between the numbers of the veins occluded in the control and test groups. Fifteen per cent of the control veins were patent, while 53 per cent of those which received heparin offered no obstruction to blood flow at the end of the experiment.

It is quite possible that if a larger series of veins had been studied with an injection of 0.15 c.c. of soricin that all of the heparinized veins would not have remained patent. The results were, however, remarkably uniform in a series of 24 veins studied. There was no obvious obstruction to blood flow in any of the 12 veins removed from animals which had received heparin. The small platelet thrombus in one of the veins was not detected before the vein was opened.

Very little further comment need be made on the nature of the obstructing mass in the vein. In many of the sections the platelets were easily demonstrable. In some cases the thrombus was composed almost entirely of platelets. It would appear that if heparinization is continued for approximately 70 hours, the intimal surfaces of the veins may heal sufficiently so that there is no danger of subsequent obstruction. In many cases the veins were removed from the animals seven days after the injury had been produced. At this time, in the obstructed vessels, the thrombus was usually firmly attached to the vein wall and showed definite evidence of organization. Recanalization might subsequently have taken place. In the vessels which were patent, the intima, in the gross, appeared normal. The microscopic findings have been described above.

It has been reported by Shionoya[14] that the administration of heparin does not prevent the formation of a white thrombus when the blood is made to pass through a collodion tube. It is possible, as Howell suggested, that large amounts of more highly purified heparin might affect this process. A study of this possibility is in progress in these laboratories.

The investigations on human cases were conducted merely to determine whether regional heparinization and general heparinization were feasible procedures with the preparations which were available. It has been shown (1) that no deleterious effects were produced in

several cases in which regional heparinization was carried out with moderately pure heparin and (2) that using highly purified material prolonged general heparinization would appear to be feasible.

If the general heparinization of patients postoperatively proceeds as satisfactorily as at present, it is hoped that a large group can be studied. We appreciate fully that before any deductions concerning the results of this procedure on the incidence of thrombus formation can be drawn, a series consisting of at least several hundred cases must be studied. A statistical treatment of the clinical findings at present available on the frequency of vascular obstruction by thrombus may indicate that this number is grossly inadequate. Furthermore, it may not be feasible to administer heparin in an intravenous infusion of saline solution to patients for more than four or five days after operation. So little is known about the factors which cause thrombosis that it is difficult to decide whether or not this is an adequate period. The times at which embolism most frequently occurs do not provide the required information since heparinization would be directed against the formation of the potential embolus. The procedures used at present, which are directed toward prevention of (1) tissue injury (liberation of thrombokinase), (2) infection, and (3) stagnation of blood, are based on sound physiologic principles, but the results of their application cannot, as yet, be considered satisfactory. While the findings we have reported in experimental animals justify the inference that clinical thrombosis, attributable to certain etiologic factors, might be prevented by heparin, it is usually impossible to determine what factors are in operation in a particular clinical case. It should be borne in mind also that heparin has not been proved to be of physiologic significance. While information on its distribution in the body and mechanism of action is available, no direct evidence indicating a physiologic rôle has been obtained.

Under these circumstances clinical research may be advantageously conducted along at least two lines: (1) attempts to determine the cases in which thrombosis is likely to occur and (2) the administration, postoperatively, for prolonged periods of a solution of highly purified heparin which increases the clotting time of the blood but produces no deleterious effects.

It is probable that attempts favorably to influence the incidence of thrombosis in postoperative cases by the administration of heparin to as many patients as possible, is not the best method of determining whether or not the anticoagulant possesses any therapeutic value. The clinical condition characterized by recurrent multiple thromboses might, for example, present a better opportunity. The use of regional or general heparinization after embolectomy in suitable cases, i.e., those in which thrombus formation would be expected at the site from which

the embolus had been removed, might give decisive results. If cases are available the effectiveness of purified heparin in these conditions will be tested.

The researches on heparin in this university were initiated in 1929 by one of us (C. H. B.) with two objectives in view. The first was to make adequate amounts of more highly purified material available for physiologic work; the second was to study the effect of the anticoagulant on thrombus formation. After some preliminary experiments with E. W. McHenry, the results of which showed that beef liver as well as dog liver was a useful source of the anticoagulant, the problem of the purification of heparin and the preparation of suitable quantities was undertaken by A. F. Charles, and D. A. Scott[15] in the Connaught Laboratories. These workers have made several reports on the results of their investigations. In their most recent paper they have described the method of preparation of a crystalline barium salt of heparin. This material consistently contains approximately 500 units per milligram. A sterile solution of this product after removal of most of the barium has been available for all of our recent investigations. We would like to acknowledge here the dependence of our work on the results obtained by Charles and Scott.

It is of great interest that Hedenius and Wilander,[16] using heparin prepared by a procedure elaborated by Charles and Scott in Toronto, have reported that the material exerts no deleterious effects in human subjects when administered intravenously in amounts which raised the clotting time well above the normal value. The effect of heparin on thrombosis was not studied, but Widström and Wilander[17] believe that they have demonstrated in experimental animals an inhibiting action of the anticoagulant on the formation of fibrin in pleural exudates.

SUMMARY AND CONCLUSIONS

1. The results of our experiments indicate that the incidence of obstruction of peripheral veins in dogs by thrombi formed as a result of certain mechanical or chemical injuries to the intimal surfaces of the blood vessels is definitely decreased when solutions of purified heparin are administered before and for prolonged periods following the injury. These findings are the results of observations on some three hundred veins.

2. The findings in the experiments in which injury was produced by chemical means suggest that the effect of heparin is clearly seen only under conditions in which the extent of the injury is just sufficient to produce thrombosis in most of the veins in animals which do not receive the anticoagulant. This statement refers to the absence of thrombus formation after heparin administration is discontinued. Thrombi have not been observed even after very severe chemical injury while the animal was well heparinized.

3. While the intimal surfaces of veins, removed from heparinized animals several days after the injection of heparin has been discontinued, may appear on macroscopic examination to have recovered completely from the injury, microscopic studies may in some cases reveal minute masses of platelets filling small crevices in the intima.

4. The clotting time of the blood of the human subject may be increased by the intravenous administration of solutions of highly purified heparin. This procedure produces no deleterious effects even when the heparinization is maintained for as long as five days. General heparinization has now been carried out in seventy-six patients postoperatively.

5. The clotting time of the blood in one limb of the experimental animal or human subject may be increased by the intraarterial administration of heparin without affecting to more than a slight degree the clotting time of the blood in other parts of the body. This is only true when the rate of injection of heparin is relatively slow.

6. Various aspects of these results and some of the directions along which further investigations may proceed are discussed.

The Banting Foundation has generously supported this investigation by making grants at various times to two of us (D. W. G. M. and T. S. P.). The kindly interest of Professor W. E. Gallie, of the Department of Surgery, and Professor J. G. FitzGerald, of the School of Hygiene, and the help in the histologic studies of Dr. D. L. MacLean are gratefully acknowledged. We are greatly indebted to Dr. O. M. Solandt for his help in some of the early experiments with sodium ricinoleate and to Dr. F. R. Wilkinson, who has made many of the recent observations on the effect of heparin on human subjects.

The expert technical assistance of Mr. Campbell Cowan has been of the greatest value.

REFERENCES

1. Zahn, F. W.: Untersuchungen über Thrombose. Bildung der Thromben, Virchows Arch. f. path. Anat. **62**: 81, 1875; Untersuchung über die Vernarbung von Querrissen der Arterienintima und Media nach vorheriger Umschnürung, Ibid. **96**: 1, 1884.
2. Eberth, J. C., and Schimmelbusch, C.: Experimentelle Untersuchungen über Thrombose, Virchows Arch. f. path. Anat. **103**: 39, 1886; Ibid. **105**: 456, 1886.
3. Welch, W. H.: Thrombosis, Papers and Addresses, Vol. I, p. 110, Baltimore, 1920, Johns Hopkins Press.
4. Zurhelle, E.: Experimentelle Untersuchungen über die Beziehungen der Infektion und der Fibringerinnung zur Thrombenbildung im strömenden Blut, Zieglers Beitr. z. path. Anat. u. z. allg. Path. **47**: 539, 1910.
5. Cannon, W. B., and Mendenhall, W. L.: Factors Affecting the Coagulation Time of Blood. I. The Graphic Method of Recording Coagulation Used in These Experiments, Am. J. Physiol. **34**: 225, 1914.
6. Stoker, S. B.: Coagulation Time of Normal Human Blood, J. Physiol. **82**: 8, 1934.
7. Jacobs, H. R. D.: An Apparatus for Constant Intravenous Injection Into Unrestrained Animals, J. Lab. & Clin. Med. **16**: 901, 1931.
8. Howell, W. H., and McDonald, C. H.: Note on the Effect of Repeated Intravascular Injections of Heparin, Bull. Johns Hopkins Hosp. **46**: 365, 1930.
9. Reed, C. I.: Practical Uses of Heparin, J. Lab. & Clin. Med. **14**: 243, 1928.
10. Mason, E. C.: A Note on the Use of Heparin in Blood Transfusion, J. Lab. & Clin. Med. **10**: 203, 1924.
11. Howell, W. H.: The Purification of Heparin and Its Chemical and Physiological Reactions, Bull. Johns Hopkins Hosp. **42**: 199, 1928.
12. Godlowski, Z.: Die Heparin-(Antiprothrombin-) Verwendung zwecks Funktionsprüfung des menschlichen retikulo-endothelialen Systems, Wien. med. Wchnschr. **83**: 1034, 1933.

13. Mason, E. C.: Blood Coagulation. The Production and Prevention of Experimental Thrombosis and Pulmonary Embolism, Surg., Gynec. & Obst. **39**: 421, 1924.
14. Shionoya, T.: Studies in Experimental Extracorporeal Thrombosis. III. Effects of Certain Anticoagulants (Heparin and Hirudin) on Extracorporeal Thrombosis and on the Mechanism of Thrombus Formation, J. Exper. Med. **46**: 19, 1927.
15. Charles, A. F., and Scott, D. A.: The Preparation of Heparin From Beef Lung, Tr. Roy. Soc. Can., Third Series, Sec. V **28**: 55, 1934; Studies on Heparin: I. The Preparation of Heparin, J. Biol. Chem. **102**: 425, 1933; II. Heparin in Various Tissues, Ibid., p. 432; III. The Purification of Heparin, Ibid., p. 437; IV. Observations on the Chemistry of Heparin, Biochem. J. **30**: 1927, 1936.
16. Hedenius, P., and Wilander, O.: The Influence of Intravenous Injections of Heparin in Man on the Time of Coagulation, Acta Med. Scandinav. **88**: 443, 1936.
17. Widström, G.. and Wilander, O.: Treatment of Experimental Pleurisy in Rabbits With Heparin, Acta Med. Scandinav. **88**: 434, 1936.

ESOPHAGEAL DIVERTICULA

With a Report of Ten Cases of the Pulsion Type Originating in the Pharynx

E. L. Eliason, M.D., Gabriel Tucker, M.D., and F. M. Thigpen, M.D.,
Philadelphia, Pa.

(From the Hospital of the University of Pennsylvania)

HISTORICAL

THE first description of a diverticulum of the esophagus was given by Ludlow in 1764, followed by later observations by Monroe in 1811, Bell in 1816, and Matthew Baille several years later. The earliest treatment was attempted dilatation of the obstructed esophagus by means of bougies. In 1848, Dendy attempted to obliterate diverticula by the use of caustics with no great success. Kluge in 1850 advocated extirpation of the sac, and Michous in 1884 was the first to accomplish this. The first operation of this type in the United States was performed by Hearn, in 1896, but not reported until three years later. Geraid, of Berne, in 1896, after two fatal operative results, devised a technic of invaginating the sac without opening the esophagus. Ten years later, Barrow perfected a method which was the forerunner of our present-day technic in which he inserted a bougie into the pouch during the operation. This, of course, has now been replaced by the esophagoscope. His treatment of the sac was essentially the same as that now used. Since that time various operations for the treatment of esophageal or pharyngeal diverticula have been devised, all of which fall into two groups, one- or two-stage operations.

In 1910, C. H. Mayo[1] performed a two-stage method and claimed that in this way the possibility of a descending mediastinitis would be lessened.

Jackson and Gaub[2] in 1915 reported two cases successfully treated by a new one-stage method. This technic has been widely adopted since that time and is the procedure of choice with many surgeons. It has been used exclusively in our clinic.

Perfecting the two-stage procedure, Judd and Mayo[3] by 1920 had accumulated a series of fifty-four cases which they reported. Both one- and two-stage methods were used in these patients with only three deaths, two following a one-stage operation, and one after the two-stage procedure. There was one recurrence and one or two cases required postoperative dilatation with bougies.

Received for publication, February 25, 1937.

Other surgeons, among them Lahey,[4] Pool,[5] Heyd,[6] and McEvers[7] have adopted and advocated the two-stage method. McEvers believes that postoperative esophageal dilatation is unnecessary. On the other hand, Lahey[4] feels that such treatment is frequently indicated to dilate the fibers of the cricopharyngeus, the constriction of which has to do with the production of the original lesion and which constriction is still present after operation.

Moynihan[7] in 1932 had operated on fifteen patients with esophageal diverticulum by the one-stage method with no complications and a perfect result in all cases. He strongly favored the one-stage operation and stated there was no reason why a competent surgeon with perfect technic should fear the dreaded complication of mediastinitis. Shallow[8] is of the opinion that pharyngeal diverticulum is a more proper name for the condition, since these pouches all really arise in the pharynx descending into the region of the upper esophagus as they increase in size. In support of this he reviews Killian's work on the anatomy of the pharynx and the possible sites of origin of these diverticula: (1) through a defect below the cricopharyngeus muscle, in the nature of a slit, through which pass the inferior branch of the recurrent laryngeal nerve, and a branch of the inferior thyroid artery; (2) above the cricopharyngeus muscle, on either the right or left side, more frequently on the left; (3) least frequently through the lowermost fibers of the inferior constricta muscle at a point pierced by another branch of the inferior thyroid artery.

Shallow[8] also reports seventy-six cases (85 per cent males and 15 per cent females) operated on by the one-stage method, with only two deaths, or a mortality of 2.6 per cent. One of his fatalities resulted from a diffuse pneumonia and the other from renal complications, the patient dying in uremia forty-eight hours after operation. He emphasizes the frequency of pulmonary complications and mentions as one factor that in many of these patients there is a preoperative bronchitis resulting from a spilling of the contents of the sac into the larynx especially when the patient is asleep. Other complications were temporary pharyngeal fistulas in five of the early cases, which has not occurred with improvement in technic; and temporary postoperative hoarseness in two cases which subsequently cleared up. There were two recurrences in his series, one in a patient who had a double diverticulum, each portion of which was removed by a separate one-stage operation, six months apart, and the other in a patient past middle age with poorly developed pharyngeal musculature. Both were reoperated upon with no recurrence after ten and three years, respectively.

McQuillan[9] reported a case of recurrent diverticulum occurring after a two-stage operation, three months previously. At operation the recurrent sac was so large that excision was impossible, and the

procedure consisted in obliterating the sac by a multiple infolding or plication of its wall, which was very thin, contrary to the usual finding. Later x-ray examination of this patient showed a beginning diverticulum on the opposite (right) side.

Corlucci[10] also reports a recurrence in a patient who had had a one-stage operation five years previously.

Torek[11] states that recurrences can take place after all types of operations on the esophagus, but that they occur less frequently after the one-stage operation. He adds that the mortality in the one-stage procedure which, 30 years previously, was extremely high, has now been reduced almost to a minimum with the perfection of the technic.

The one-stage operation has been used exclusively at the hospital of the University of Pennsylvania with uniformly good results.

CASES OF ESOPHAGEAL DIVERTICULUM OPERATED UPON BY ELIASON AND TUCKER, 1922 TO 1934

This series is composed of ten cases operated upon during a twelve-year period, from 1922 to 1934, and is reported from the combined surgical service of E. L. Eliason and the bronchoscopic service of Gabriel Tucker at the hospital of the University of Pennsylvania.

Of the ten patients, seven were males, ranging in age from forty-two to seventy years, and three females, from sixty-five to sixty-eight years, the average age for the entire group being 58.5 years. From this it would seem that the condition is more frequent in males and occurs at an earlier age, except in one instance, in males.

The chief symptoms were those usually described in association with this condition, namely, dysphagia, regurgitation of liquids, and as the condition became worse, of solid food, always more marked when lying down, and cough. Hoarseness occurred in two cases, and in two there was marked weight loss. One patient complained of a burning sensation in the pharynx. The duration of symptoms varied considerably, the longest period being fifteen years, and the shortest four months, with an average length of time of four years. In only one was there palpable fullness of the lower neck, and in this case pressure over this area produced a gurgling sound. The Boyce sign of pulsion diverticulum was positive in each case.

All patients were examined roentgenologically with both films and fluoroscopic study with and without an opaque mixture in order to establish the location and size of the pouch. Esophagoscopic examination was made of the pouch and the hypopharynx to exclude ulceration either benign or malignant. The patient was then given a string to swallow. When this had passed far enough into the small bowel to be firmly anchored when pulled upon, it was used as a guide to find the orifice of the subdiverticular esophagus. The opening into the subdiverticular esophagus is just in front of the neck of the pouch,

and it is very difficult to find in many cases. The esophagoscope was passed over the taut string and the opening of the esophagus in the pharynx and the entire subdiverticular esophagus were carefully examined to exclude ulceration, stricture, or other intrinsic lesions. These examinations are routine in every case and definitely establish the diagnosis and give an impression of size, character, and location of the diverticulum and reveal or exclude evidences of other disease of the esophagus which might be an important consideration in connection with the operative procedure.

The anesthesia employed in the first five cases was ether by intratracheal administration, and in the last five, avertin, and local, which has proved more satisfactory.

A one-stage operation was performed in all of these cases with the aid of the esophagoscope, using the technic devised by Jackson and Gaub.

In one case, because of the very large size of the pouch and its pressure on the subdiverticular esophagus, the patient was unable to take liquids in sufficient quantity for proper nourishment and came into the hospital in very poor general condition. In this case a string was swallowed, the esophagoscope passed over the swallowed string, and a feeding tube put in the stomach. The esophagoscope was removed leaving the tube and string in position and the upper end of the feeding tube was brought through the pharynx and anterior nares. The string and feeding tube were allowed to remain in the esophagus for several weeks until the patient's general condition became such as to justify operative excision of the diverticulum. At the time esophagoscopic aid was given during the excision of the diverticulum, the feeding tube was allowed to remain in position, and it was found that it was much easier to enter the subdiverticular esophagus over the string with the feeding tube already placed. Also during withdrawal of the esophagoscope, the site of excision and inversion of the neck of the sac in the pharynx could be inspected satisfactorily with the esophagoscope. This led us to modify the procedure as follows:

THE IMPROVED PROCEDURE OF ESOPHAGOSCOPIC AID

After x-ray study with both films and fluoroscopy with the use of an opaque mixture the patient is given a No. 14 twisted silk thread with a frayed end, fifteen feet in length. The end of the string is swallowed slowly with small amounts of water until thirteen feet have entered the esophagus. This should consume about a thirty-six-hour period. The remaining two feet are then anchored outside the mouth so that the string cannot be completely swallowed and after forty-eight hours have elapsed the esophagoscopic examination is made. The esophagoscope is first passed into the pharynx and the

diverticular pouch is carefully examined. Usually a considerable quantity of retained food is evacuated in order to inspect the interior of the pouch. The esophagoscope is then withdrawn and passed over the string which is pulled taut and followed as a guide into the entrance of the subdiverticular esophagus. The entire esophagus is carefully examined and a feeding tube, No. 14 Levin, is passed through the esophagoscope alongside the string. The esophagoscope is withdrawn leaving the string and feeding tube in position, and the upper end of the feeding tube is brought out through the nose where it remains until after the operative procedure of excision of the sac. The string is fastened outside the mouth so it will not be completely swallowed.

ESOPHAGOSCOPIC AID DURING EXCISION OF THE POUCH

After external incision in the neck and exposure of the pouch by the surgeon, the esophagoscope, 8 mm. full lumen by 45 cm., is introduced into the pharynx and the pharynx and pouch are emptied. Under the guidance of the surgeon from the wound in the neck, the pouch is carried gently outward until it is visible in the open wound. Transillumination with the esophagoscope will show the limits of the pouch. The bottom of the pouch is grasped with an Allis type forceps by the surgeon and pulled outward and separated from the esophagus. The esophagoscope is withdrawn as the pouch is pulled outward until the neck of the diverticulum is reached. Then the esophagoscope is entirely withdrawn and threaded over the previously swallowed string and reintroduced with the string as a guide avoiding the location of the diverticular pouch. The string is followed alongside of the feeding tube, which has remained in position and which also assists in the passage of the esophagoscope into the subdiverticular esophagus. The sac is then withdrawn into the wound by the surgeon who excises enough to eliminate the pouch formation. The neck of the sac is inverted or excised as the surgeon may desire. The esophagoscope in the subdiverticular esophagus prevents excision of too great an amount of the redundant esophagus in the neighborhood of the pouch. After the sac is removed, the string is cut and pushed into or withdrawn from the stomach and the esophagus at the site of the excision of the pouch is carefully inspected as the tube is removed. The feeding tube remains in place.

The advantages of the modified esophagoscopic technic are: first, the feeding tube assists in getting the esophagoscope into the subdiverticular esophagus and; second, the site of excision of the diverticulum is inspected as the esophagoscope is withdrawn.

The technic is as follows: After exposure of the sac by means of an incision along the anterior border of the left sternocleidomastoid

muscle (all of the diverticula presented to the left, as is usually the case), the esophagoscope was then inserted into the hypopharynx and pouch thus facilitating its dissection and immobilization and preventing the dissection from being carried too far. It was necessary to ligate the inferior thyroid artery in one instance. Shallow[8] found this procedure necessary in 35 per cent of his cases, one double diverticulum being caused by the presence of the artery. The esophagoscope was then withdrawn and introduced over the previously swallowed string into the subdiverticular esophagus. The sac was crushed about a centimeter from its base using a small Payr clamp and the excess removed by means of the actual cautery passed along the distal edge of the clamp. The stump was then inverted by from three to five rows of interrupted mattress sutures of fine chromic catgut. In no instance did esophageal obstruction result. The fascia and skin were then closed in layers in an appropriate manner. In two cases the sac was quite small and simple inversion without excision of the pouch was carried out, since it was apparent that no obstruction would result. The feeding tube was allowed to remain in position for purposes of feeding during the first few postoperative days. Drainage was employed in all cases, using the cigarette or Penrose type of drain. The wounds closed promptly after removal of the drains on the third to fifth postoperative day, except in one case, in which there was persistent foul discharge for ten days but subsequent satisfactory healing. The skin sutures were removed usually on the fifth or sixth postoperative day.

The postoperative treatment in these cases consisted in administration of an adequate liquid diet of high caloric value for seven to ten days, the last three or four days of which period part of the liquids were given by mouth, if well tolerated, in gradually increasing amounts. The tube was removed on the eighth to tenth day and soft diet allowed. The patients were usually allowed out of bed on the eleventh to fifteenth day, depending on their general condition and the degree of healing of the wound, and discharged one or two days later.

No evidence of malignancy in any of the diverticula could be found at the esophagoscopic examination or later by the pathologist. Shallow[8] reports one such case. Nine of these patients lived and there was one death, giving a mortality of 10 per cent.

The one death occurred in the case of a woman sixty-eight years of age who developed atelectasis thirty-six hours after operation and later pneumonia, and who died on the fifth postoperative day, despite adequate oxygen therapy, nourishment by Jutte tube, respiratory exercises, and circulatory stimulants. At postmortem examination there was found atelectasis of the lower lobe of the left lung, lobar

pneumonia of the right upper lobe, and bronchopneumonia of the right lower lobe. The examination was limited to examination of the thorax through an abdominal incision and hence the operative site could not be inspected.

Other complications in this series were: persistent drainage from the operative site in one case as mentioned; paroxysmal auricular fibrillation in one case, controlled by digitalis; and temporary paralysis of the left vocal cord, secondary to injury of the left recurrent laryngeal nerve, in two cases. One of these cleared up before the patient left the hospital and the other soon after discharge. In none of the patients did a mediastinitis occur.

TABLE SHOWING COMPLICATIONS

Prolonged drainage	1
Auricular fibrillation	1
Temporary paralysis of vocal cord	2

The temporary paralysis of the vocal cord was due to stretching of the recurrent nerve on the left side during the operation and was completely recovered within one month of the operation in each case.

FOLLOW-UP

The end-results in the majority of these nine patients who recovered from operation were quite satisfactory.

Two patients were followed for four months and six months respectively and both were entirely symptom-free at the end of these periods; neither returned for subsequent visits nor can they be reached by letter.

One patient was completely relieved for one year after operation and since then was not heard from until a recent reply to a questionnaire. In this he states that there was a recurrence of symptoms after the first year and that he has continued to suffer some degree of discomfort. This cannot be taken as conclusive evidence of a failure, since the patient was not personally seen and examined.

Five patients have been followed for periods of from one to six years and all are perfectly well, most of them showing marked weight gain in addition to relief of all symptoms.

One patient did not return for follow-up examination and no information can be obtained concerning him.

TABLE SHOWING END-RESULTS

Completely cured, less than one year	2
Completely cured, one to six years	5
Cured for one year, probable recurrence	1
No follow-up	1
Death	1

SUMMARY AND CONCLUSIONS

1. A series of ten cases of esophageal diverticulum operated upon by the one-stage method is reported in which there was one death, or a mortality of 10 per cent.

2. The majority of the patients were males, and with one exception, the condition occurred at an earlier age in the ten males than in the three females.

3. The chief symptoms of the condition are dysphagia, regurgitation, and cough.

4. Diagnosis of esophageal diverticulum should be confirmed preoperatively by films and fluoroscopic study with an opaque mixture and by esophagoscopic examination.

5. The procedure of choice is the one-stage operation with the aid of the esophagoscope, anesthesia being avertin and local.

6. In none of the patients did a mediastinitis occur.

7. Eight of the nine patients who recovered have been followed and seven of these are perfectly well, or were, when last heard from. There has been a probable recurrence in one case.

8. Postoperative bouginage was not required in any case.

REFERENCES

1. Mayo, C. H.: Diagnosis and Treatment of Esophageal Diverticula, Ann. Surg. **51**: 812, 1910.
2. Gaub, O., and Jackson, Chevalier: Pulsion Diverticulum of the Esophagus, a New Operation for Its Cure, Surg., Gynec. & Obst. **21**: 52, 1915.
3. Judd, E. S.: Esophageal Diverticulum, Arch. Surg. **1**: 18, 1920.
4. Lahey, F. H.: Diverticulum of the Esophagus in "Brief Communications," Ann. Surg. **95**: 797, 1932.
5. Pool, E. H.: Diverticulum of the Esophagus, Two Stage Operation, Ann. Surg. **95**: 151, 1932.
6. Heyd, G. G.: Diverticulum of the Esophagus, Two Stage Operation, S. Clin. North America **9**: 515, 1929.
7. Moynihan, Sir Berkeley: Correspondence, Surg., Gynec. & Obst. **54**: 128, 1932.
8. Shallow, T. A.: Combined One Stage Closed Method for the Treatment of Pharyngeal Diverticula, Surg., Gynec. & Obst. **62**: 624, 1936.
9. McQuillan, A. S.: Transaction of the New York Surgical Society, Ann. Surg. **97**: 299, 1933.
10. Corlucci, G. A.: Ibid.
11. Torek, Franz: Ibid.

PERFORATION OF THE GASTROINTESTINAL TRACT: AN EXPERIMENTAL STUDY OF FACTORS INFLUENCING THE DEVELOPMENT OF PERITONITIS*

GEORGE S. BERGH, M.D., WARNER F. BOWERS, M.D., AND OWEN H. WANGENSTEEN, M.D., MINNEAPOLIS, MINN.

(From the Department of Surgery, University of Minnesota)

PERFORATION of the gastrointestinal tract following trauma or as a result of pathologic processes originating within the digestive canal is encountered frequently in clinical medicine and surgery. The seriousness of such an accident is well known.

The observation that fasting animals withstand experimental perforation better than animals which recently have taken food stimulated us to undertake a study of some of the factors influencing the development of peritonitis following perforation.

Soiling of the peritoneal cavity follows the escape of the contents of the stomach or intestine and, in accordance with the general bacteriologic rule, the degree of infection which will occur under such circumstances depends upon the number and virulence of the escaping organisms and upon the local and general resistance of the host.

The number of organisms escaping is influenced by several factors: the size of the perforation, the length of time it remains open, and the forces tending to carry contents of the viscus out into the peritoneal cavity are important, as well as the number of viable, pathogenic bacteria and the amount and fluidity of material present in the viscus at the level of perforation. Factors influencing the virulence of microorganisms are not well understood.

Factors influencing the general resistance of the host are likewise complex. Local resistance, however, may be affected by the juices escaping from the intestinal tract.

METHOD

Under pentobarbital-sodium anesthesia and with aseptic precautions, perforations were established at various levels of the gastrointestinal tract of laboratory animals after periods of fasting and also following the ingestion of food. A total of one hundred and forty-five animals were used.

Most of the perforations of the stomach consisted of unsutured linear incisions one centimeter in length, but in a few cases a circular defect was made. As indicated in the tables, the incisions were made in various regions of the viscus.

*Aided by a grant from the Research Funds of the Graduate School, University of Minnesota.

Received for publication, March 8, 1937.

In some animals perforation was accomplished by means of a sharp brass pipe passed through the esophagus. After the induction of anesthesia, a sterilized rubber tube was passed perorally into the stomach which was then perforated by a sterilized, sharpened, metal pipe passed through the rubber tube (Fig. 1). Such perforations occurred at the greater curvature. When it was desired to permit an easy escape of stomach contents into the peritoneal cavity, a pipe with numerous, fairly large openings in its wall was used (Fig. 2). Studies by Borman and Bergh have demonstrated that when the latter type of pipe is used, fluid contents of the stomach invariably escape into the peritoneal cavity and pneumoperitoneum sometimes results, while there is practically no escape when the solid-walled pipe is used.

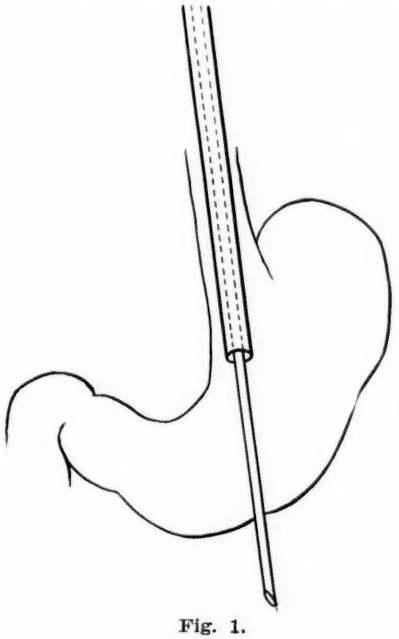

Fig. 1.

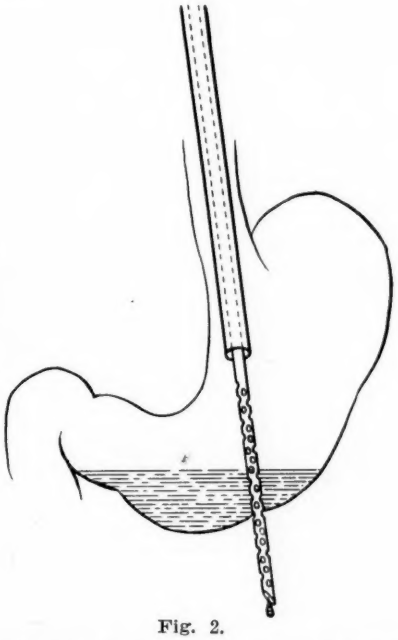

Fig. 2.

Fig. 1.—Method of perforating the stomach with a solid-walled pipe without performing laparotomy.

Fig. 2.—Method of perforating the stomach with a pipe which allows stomach contents to escape.

In some animals an attempt was made to simulate the edema and inflammatory changes which exist around peptic ulcers by the preliminary injection of a sclerosing solution (proliferol). One to three cubic centimeters of the sclerosing solution were injected into the antral wall and the viscus was perforated through this area several days later.

In studying intestinal perforations, we used fasted animals exclusively, the period of starvation ranging from one to three days. Most perforations consisted of an unsutured incision one centimeter in length in the axis of the bowel along the antimesenteric border. Transverse incisions were made in some cases, but the results did not differ from the others.

All animals were observed for signs of peritonitis and those which died were subjected to autopsy. Many of the surviving animals were sacrificed or operated upon to observe the healing process. Bacteriologic studies were made in cases in which peritonitis developed.

RESULTS

I. Perforation of the empty stomach was carried out in twenty-nine animals. In this series there were two deaths from peritonitis, a mortality of 6.9 per cent (Table I). In one of the two fatal cases a large

TABLE I

PERFORATION OF EMPTY STOMACH (MORTALITY 6.9%)

ANIMAL	FATE	TYPE OF PERFORATION	REMARKS
Dog 1	Survived	1 cm. incision in anterior wall	No water for 24 hr.; no food for 48 hr. Sacrificed in 12 days. Healed. No peritonitis
2	Survived	1 cm. incision in anterior wall	Same regime. Sacrificed in 4 days. No peritonitis
3	Survived	1 cm. incision in anterior wall	Food and water at will. Sacrificed in 6 days. No peritonitis.
4	Survived	1 cm. incision in anterior wall	Same regime. Sealed in 48 hr.
5	Survived	1 cm. incision in anterior wall	Same regime. Sealed in 24 hr.
6	Survived	1 cm. incision in anterior wall	Same regime. Sealed in 3 days
7	Survived	1 cm. incision in anterior wall	Not sacrificed
8	Survived	1 cm. incision in anterior wall	Sacrificed in 5 days. Healed
9	Survived	1 cm. incision in anterior wall	Not sacrificed
10	Survived	1 cm. incision in anterior wall	Not sacrificed
11	Died 72 hr.	1 cm. incision in anterior wall	Perforation not healed. Generalized peritonitis. Gram + streptococci, staphlococci, and rods
12	Survived	1 cm. incision in anterior wall	Not sacrificed
13	Survived	1 cm. incision in anterior wall	Not sacrificed
14	Survived	1 cm. incision in fundus	Not sacrificed
15	Survived	1 cm. incision in fundus	Not sacrificed
16	Survived	1 cm. incision in fundus	Not sacrificed
17	Survived	1 cm. incision in fundus	Not sacrificed
18	Survived	1 cm. incision in posterior wall	Not sacrificed
19	Survived	1 cm. incision in posterior wall	Not sacrificed
20	Survived	1 cm. incision in posterior wall	Not sacrificed
21	Survived	1 cm. incision in posterior wall	Not sacrificed
22	Survived	Circular defect, 0.5 cm. diameter	Not sacrificed
23	Survived	Circular defect, 0.5 cm. diameter	Not sacrificed
24	Died 24 hr.	Circular defect, 1.5 cm. diameter	Perforation open. Severe peritonitis. Gram + rods and streptococci
25	Survived	Sharpened pipe—solid walled	Examination in one week. Perforation healed. No peritonitis
26	Survived	Sharpened pipe—solid walled	Same. No peritonitis
27	Survived	Sharpened pipe—solid walled	Same. No peritonitis
Cat 28	Survived	1 cm. incision in anterior wall	Not sacrificed
29	Survived	1 cm. incision in anterior wall	Not sacrificed

circular defect (1.5 cm.) had been established, and in the other the linear perforation had remained open. In the remaining animals the perfora-

tion closed itself almost immediately and within twenty-four hours was well sealed by fibrinous exudate. In the earliest experiments water was withheld for twenty-four hours and food for forty-eight hours, but in later studies the animals were allowed to take food and water at will without ill effects.

There appeared to be no relationship between the location of the perforation in the stomach wall and the development of peritonitis. The type of perforation was likewise unimportant unless a large defect were made, in which case spontaneous closure of the opening would be less likely to occur.

II. Perforation of the stomach containing food was performed in thirty animals—thirteen dogs, five cats, ten rabbits, and two guinea pigs (Table II). In this series there were twenty-six deaths from

TABLE II

PERFORATION OF STOMACH CONTAINING FOOD BY MEANS OF AN INCISION 1 CM. IN LENGTH IN THE ANTERIOR WALL (MORTALITY 86.7%)

ANIMAL	FATE	BACTERIOLOGY	REMARKS
Dog 30	Survived		Sacrificed. No peritonitis
31	Died 24 hr.	*B. subtilis* and *B. welchii*	Generalized peritonitis
32	Died 24 hr.		Generalized peritonitis
33	Died 24 hr.	Gm. + rods, cocci, and streptococci	Perforation open
		Gm. - rods	Generalized peritonitis
34	Died 96 hr.	Gm. + rods and streptococci	Generalized peritonitis
		Gm. - rods	
35	Died 24 hr.	Same organisms	Generalized peritonitis
36	Died 24 hr.	Same organisms	Generalized peritonitis
37	Died 72 hr.	Same organisms	Generalized peritonitis
38	Died 24 hr.	Same organisms	Generalized peritonitis
39	Died 48 hr.	Same organisms	Generalized peritonitis
40	Died 24 hr.	Same organisms	Generalized peritonitis
41	Died 24 hr.	Gm. + and Gm. - rods	Generalized peritonitis
42	Died 24 hr.	Gm. + rods, diplococci, and staphylococci	Generalized peritonitis
Cat 43	Died 24 hr.	Gm. + rods, streptococci, and Gm. - rods	Parasites extruding
			Generalized peritonitis
44	Died 24 hr.	Gm. + rods and streptococci	Generalized peritonitis
45	Died 48 hr.	Gm. + and Gm. - rods	Generalized peritonitis
46	Died 9 days	Gm. + anaerobes, rods, and streptococci	Generalized peritonitis
47	Died 24 hr.	Gm. + anaerobes, rods, and streptococci	Generalized peritonitis
Rabbit 48	Survived		Gastrojejunal fistula
49	Survived		Perforation healed
50	Died 24 hr.		Generalized peritonitis
51	Died 24 hr.		Generalized peritonitis
52	Died 24 hr.		Generalized peritonitis
53	Died 24 hr.		Generalized peritonitis
54	Died 24 hr.		Generalized peritonitis
55	Died 24 hr.		Generalized peritonitis
56	Died 24 hr.		Generalized peritonitis
57	Died 5 days		Generalized peritonitis
Guinea pig 58	Died 3 days		Generalized peritonitis
59	Survived		Sealed by omentum. No peritonitis

peritonitis, a mortality of 86.7 per cent. Only one of the thirteen dogs survived, and nine of the twelve deaths occurred within twenty-four hours after the perforation. The rabbit's stomach was found to contain ingesta even after prolonged periods of fasting. Eight of the ten rabbits died from peritonitis. One of the survivors developed a spontaneous gastrojejunal fistula at the point of perforation, and in the other the perforation was sealed by omentum. Fatal peritonitis developed in all five cats and in one of the guinea pigs.

Bacteriologic studies of the peritoneal exudate revealed the presence of a variety of organisms (Table II).

III. Perforation of the stomach of fasting dogs immediately before and after the administration of liquids was carried out in seventeen animals, with three deaths from peritonitis, a mortality of 17.6 per cent (Table III). Except when the anesthesia was light, allowing the animal to strain, minimal amounts of the liquid escaped into the peritoneal cavity. The intragastric tension did not increase in proportion to the

TABLE III

PERFORATION OF STOMACH OF FASTING DOGS IMMEDIATELY BEFORE AND AFTER THE ADMINISTRATION OF LIQUIDS (MORTALITY 17.6%)

DOG	FATE	PROCEDURE	REMARKS
60	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
61	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
62	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
63	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
64	Died 24 hr.	Perforated—200 c.c. water instilled	Generalized peritonitis—Gm. + rods, diplococci, and staphylococci and Gm. - rods
65	Survived	Perforated—200 c.c. water instilled	No peritonitis
66	Survived	Perforated—200 c.c. water instilled	No peritonitis
67	Survived	Drank 200 c.c. milk—perforated—not aspirated	No peritonitis
68	Survived	Drank 200 c.c. milk—perforated—not aspirated	No peritonitis
69	Survived	Drank 200 c.c. milk—perforated—not aspirated	No peritonitis
70	Survived	Drank 200 c.c. milk—perforated—not aspirated	No peritonitis
71	Died 24 hr.	Given 500 c.c. milk—perforated—not aspirated	Generalized peritonitis
72	Survived	Given 500 c.c. milk—perforated—not aspirated	No peritonitis
73	Survived	Given 500 c.c. milk—perforated—not aspirated	No peritonitis
74	Died 24 hr.	Given 500 c.c. milk plus barium—perforated—not aspirated	Generalized peritonitis—Gm. + rods, streptococci, and diplococci and Gm. - rods
75	Survived	Given 500 c.c. milk plus barium—perforated—not aspirated	No peritonitis
76	Survived	Given 500 c.c. milk plus barium—perforated—not aspirated	No peritonitis

amount of liquid administered, since the stomach walls are able to accommodate themselves to the volume of gastric contents without increasing the pressure. Straining, however, did increase the intragastric tension sufficiently to force fluid from the stomach into the peritoneal cavity. Peristalsis did not cause stomach contents to be forced out through the perforation.

The perforation in dogs 60 to 70 was carried out by means of the metal pipe with openings in its wall (Fig. 2). The others were perforated by means of an unsutured linear incision. The first method permits x-ray examination for pneumoperitoneum, but when laparotomy has been carried out the presence of gas in the peritoneal cavity is without significance.

IV. Perforation of the empty stomach through an area previously injected with a sclerosing solution was carried out in ten dogs (Table IV). Four of these animals died from peritonitis, a 40 per cent mortal-

TABLE IV

PERFORATION OF EMPTY STOMACH OF THE DOG. PROLIFEROL INJECTED INTO WALL (MORTALITY 40%)

DOG	AMOUNT INJECTED	INTERVAL BEFORE PERFORATION	FATE	BACTERIOLOGY	REMARKS
77	2 c.c.	3 days	Survived		
78	2 c.c.	3 days	Survived		
79	1 c.c.	3 days	Survived		
80	2 c.c.	3 days	Survived		
81	2 c.c.	5 days	Survived		
82	2 c.c.	30 days	Survived		Very little induration
83	2 c.c.	5 days	Died 24 hr.	Gm. + rods and cocci, and Gm. - rods	Generalized peritonitis. Perforation open
84	3 c.c.	3 days	Died 6 days	Mixed organisms	Generalized peritonitis. Perforation open
85	1 c.c.	3 days	Died 7 days	Mixed organisms	Generalized peritonitis. Perforation open
86	2 c.c.	5 days	Died 6 wk.	Gm. + rods, streptococci, and spore formers, and Gm. - rods	Exudate over perforation. Much free fluid in the peritoneal cavity. Low grade peritonitis

ity. Autopsies revealed that the perforations had failed to heal in the fatal cases. There was no definite correlation between the amount of solution injected or the interval elapsing before perforation and the mortality rate. The edema and infiltration produced by the injection is the closest experimental approach to the conditions existing in the presence of peptic ulcer.

V. Perforation of the duodenum was established in sixteen dogs, with a mortality of 81.2 per cent from peritonitis (Table V). In twelve an-

TABLE V

PERFORATION OF DUODENUM OF DOG
(FASTING ANIMALS)
(MORTALITY 81.2%)

DOG	LEVEL	FATE	BACTERIOLOGY	REMARKS
87	1 cm. from pylorus	Died 96 hr.	Gm. + spore formers, rods, and streptococci, and Gm. - rods	Parasites extruding Generalized peritonitis
88	1 cm. from pylorus	Died 24 hr.		Perforation open Generalized peritonitis
89	3 cm. from pylorus	Died 24 hr.		Perforation open Generalized peritonitis
90	Midpancreas	Died 36 hr.		Perforation open Generalized peritonitis
91	Midpancreas	Died 48 hr.		Perforation open Generalized peritonitis
92	Midpancreas	Died 3 wk.		Peritonitis at 1 week Sealed by exudate Died of pneumonia
93	Midpancreas	Survived		
94	Tail of pancreas	Died 96 hr.	Gm. + rods, staphylococci, and streptococci, and Gm. - rods	Perforation open Generalized peritonitis
95	Tail of pancreas	Died 24 hr.	Gm. + anaerobes, rods, and spore formers. Gm. - rods	Perforation open Generalized peritonitis
96	Tail of pancreas	Survived		Signs of peritonitis early, but recovered
97	Tail of pancreas	Died 24 hr.		Perforation open Generalized peritonitis
98	Tail of pancreas	Died 72 hr.	Gm. + spore formers and rods. Gm. - rods	Perforation open Generalized peritonitis
99	Midpancreas	Survived		Transverse incision Laparotomy at one week revealed fat necrosis
100	Midpancreas	Died 24 hr.		Transverse incision, open—peritonitis
101	Midpancreas	Died 72 hr.	Mixed organisms	Transverse incision, open—peritonitis
102	Midpancreas	Died 72 hr.	Mixed organisms	Transverse incision, open—peritonitis

imals a longitudinal incision was made on the antimesenteric border at levels varying from one centimeter from the pylorus to the level of the tail of the pancreas. Ten of these animals expired. One of the survivors showed signs of peritonitis but recovered. In four dogs a transverse incision was used. Three of these animals died from peritonitis. The survivor was sacrificed in one week and showed marked fat necrosis throughout the peritoneal cavity.

VI. Perforation of the jejunum at distances varying from fifteen to ninety centimeters from the duodenojejunal angle was carried out in nine dogs. The mortality rate from peritonitis was 44.4 per cent (Table VI). There was no definite relationship between the level of perforation and the mortality rate.

In three dogs the Exalto-Mann-Williamson operation was performed in the hope of producing ulcers that might be experimentally

TABLE VI

PERFORATION OF JEJUNUM OF DOG
(FASTING ANIMALS)
(MORTALITY 44.4%)

DOG	DISTANCE FROM THE DUODENO-JEJUNAL ANGLE	FATE	BACTERIOLOGY	REMARKS
103	15 cm.	Died 48 hr.	Gm. + diplococci, rods, and Gm. - rods	Perforation open Generalized peritonitis
104	45 cm.	Died 24 hr.	Gm. + and Gm. - rods	Perforation open Generalized peritonitis
105	45 cm.	Survived		
106	60 cm.	Survived		
107	60 cm.	Died 24 hr.	Gm. + spore formers, rods, streptococci, and Gm. - rods	Perforation open Generalized peritonitis
108	60 cm.	Survived		
109	75 cm.	Died 24 hr.	Gm. + spore formers, rods, and streptococci, and Gm. - rods	Perforation open Generalized peritonitis
110	90 cm.	Survived		
111	90 cm.	Survived		

perforated. At the time of reoperation, however, no ulcers were found. The jejunum was, therefore, perforated by a linear incision just distal to the anastomosis (fasting animals). The animals all survived jejunal perforation, and one animal was so perforated on three occasions. Two of the animals subsequently died of spontaneous perforation of jejunal ulcers following a meal.

VII. Perforation of the lower ileum was performed in nine dogs (Table VIII). All of these animals died from peritonitis within seventy-

TABLE VII

JEJUNAL PERFORATION IN EXALTO-MANN-WILLIAMSON DOGS
BEYOND GASTROJEJUNAL ANASTOMOSIS
(FASTING ANIMALS)
(MORTALITY 0%)

DOG	FATE	REMARKS
112	Survived	No ulcer at 1 month. Jejunum incised at 1 month. Healed. Three weeks later dog died of spontaneous perforation of jejunal ulcer.
113	Survived	Jejunum incised at 1 month, 3 months, and 5 months. Healed each time. No ulcer developed during period of observation.
114	Survived	Jejunum incised at 3 weeks. No peritonitis. Animal died three months later of spontaneous perforation of a jejunal ulcer.

two hours, a mortality of 100 per cent. Autopsy revealed that the perforation had remained open in every case.

VIII. Perforation of the large bowel was carried out at three levels: the cecum, descending colon, and rectum.

TABLE VIII

PERFORATION OF LOWER ILEUM OF DOG, 24 CM. PROXIMAL TO CECUM
(FASTING ANIMALS)
(MORTALITY 100%)

DOG	FATE	BACTERIOLOGY	AUTOPSY
115	Died 24 hr.	Gm. + rods, spore formers, and short chained streptococci. Gm. - rods	Perforation open Generalized peritonitis
116	Died 24 hr.	Gram positive rods	Perforation open Generalized peritonitis
117	Died 24 hr.	Gm. + rods, short chained streptococci, and rare Gm. negative rods	Perforation open Generalized peritonitis
118	Died 24 hr.	Gm. + anaerobes, rods, staphylococci, and streptococci, and Gm. - rods	Perforation open Generalized peritonitis
119	Died 48 hr.	Gm. + anaerobes, rods, many streptococci, few staphylococci, Gm. - rods	Perforation open Generalized peritonitis
120	Died 48 hr.	Gm. + diplococci, streptococci, and rods. Rare Gm. - rods	Perforation open Generalized peritonitis
121	Died 48 hr.	Gm. + rods, rare spore formers, and rare Gm. - rods	Perforation open Generalized peritonitis
122	Died 72 hr.	Gm. + anaerobes, diplococci, and rods Few Gm. - rods	Perforation open Generalized peritonitis
123	Died 72 hr.	Gm. + anaerobes, diplococci, and rods	Perforation open Generalized peritonitis

In seven dogs in which the cecum was perforated, two died, a mortality of 28.5 per cent (Table IX). An identical mortality was found (28.5%) in a similar series of perforations of the descending colon (Table X).

TABLE IX

PERFORATION OF CECUM OF DOG
(FASTING ANIMALS)
(MORTALITY 28.5%)

DOG	FATE	AUTOPSY
124	Survived	Perforation healed without adhesions
125	Survived	Perforation healed without adhesions
126	Survived	Perforation healed without adhesions
127	Survived	Perforation healed without adhesions
128	Survived	Perforation healed without adhesions
129	Died 24 hr.	Perforation open. Generalized peritonitis. Gm. + rods and streptococci, and Gm. - rods
130	Died 36 hr.	Perforation open. Generalized peritonitis. Mixed organisms

TABLE X

PERFORATION OF DESCENDING COLON OF DOG
(FASTING ANIMALS)
(MORTALITY 28.5%)

DOG	FATE	AUTOPSY
131	Survived	Not sacrificed
132	Survived	Not sacrificed
133	Survived	Not sacrificed
134	Survived	Not sacrificed
135	Survived	Not sacrificed
136	Died 24 hr.	Perforation open. Generalized peritonitis. Gram positive rods and streptococci and gram negative rods
137	Died 72 hr.	Perforation open. Peritonitis. Mixed organisms

In eight animals the rectum was perforated by means of a scalpel introduced through the anus (Table XI). Perforation into the

TABLE XI

PERFORATION OF RECTUM OF DOG
(FASTING ANIMALS)
(MORTALITY 12.5%)

DOG	FATE	REMARKS
138	Survived	Perforated through anus. Sacrificed in 1 week. No peritonitis. No adhesions
139	Survived	Perforated through anus. Sacrificed in 5 days. No peritonitis. No adhesions
140	Survived	Perforated through anus. No peritonitis
141	Survived	Perforated through anus. No peritonitis
142	Survived	Perforated through anus. No peritonitis
143	Survived	Perforated through anus. No peritonitis
144	Survived	Perforated through anus. No peritonitis
145	Died 24 hr.	Perforated through anus. Severe generalized peritonitis. Mixed organisms

peritoneal cavity was verified in each instance by abdominal exploration. Only one animal succumbed, a mortality of 12.5 per cent. The others showed a small linear scar without the formation of adhesions.

DISCUSSION

The degree of infection which will develop following perforation of the gastrointestinal tract depends upon the number and virulence of the escaping organisms and upon the local and general resistance of the host.

Bacteriologic studies by various investigators[3, 8] have shown that the gastrointestinal tract is free from bacteria at the time of birth. The ingestion of organisms with the food, however, soon leads to the establishment of an abundant intestinal flora, and it has been estimated that a normal adult excretes daily in the feces nearly thirty trillion bacteria.[8] The food itself does not contain this large number of organisms, but there is bacterial proliferation within the alimentary canal.

Studies of the contents of the gastrointestinal tract a few hours after a meal[3, 5] have revealed the presence of a fairly large number of organisms in the stomach. There is a pronounced diminution in number in the duodenum, with a gradual increase to the region of the ileocecal valve where the number is the greatest. In the large intestine there is a marked decrease in the number of bacteria. The variety of organisms is great but the colon bacillus is the predominant type.

Gilbert and Dominici[5] determined the number of organisms in different parts of the alimentary canal of dogs two and a half and three hours after a meal of bread and meat. Their findings are summarized in a diagram which is reproduced in Fig. 3.

The acid gastric juice exerts a deleterious effect upon bacteria and gradually decreases the number of organisms in the stomach. In the duodenum there is a distinct decrease in the relative number of bacteria, probably due to the dilution of the chyme by the biliary

and pancreatic fluids.[5] As the chyme passes downward, however, there is a multiplication of the bacteria which find more favorable conditions for growth as they escape the pronounced acidity of the upper portion of the canal.

After a period of starvation, the number of organisms is greatly diminished and the stomach and duodenum become relatively amicrobic.[3] Lower in the intestine, however, there remain a considerable number of bacteria even after a prolonged fast. Kendall[8] found a large number of colon bacilli in the large intestine of a man who had fasted for thirty days.

We found that openings in the normal stomach wall seal themselves soon after perforation and leakage occurs for only a very short time. When there is no food present, very little material escapes, and that which does reach the peritoneal cavity contains relatively few organisms. When the stomach contains food, however, enough material is likely to escape, even in a short time, to institute a severe infection of the peritoneal cavity. The mortality in such cases is

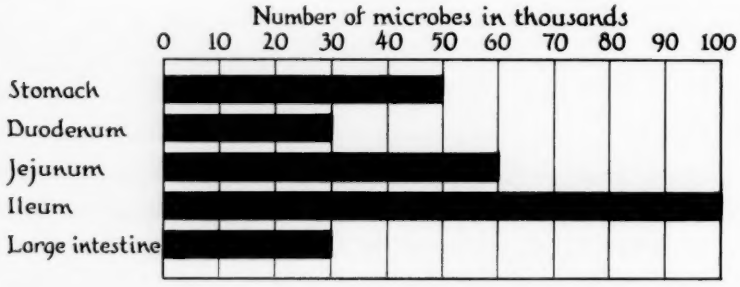

Fig. 3.—Relative number of bacteria in various parts of the alimentary canal of the dog, according to Gilbert and Dominici.

high, but if the infection is not overwhelming the animal may survive. Several dogs were able to withstand the escape of moderate amounts of milk or water (fluids which contain relatively few pathogenic bacteria) into the peritoneal cavity. Our results, however, differ from those of Himmelmann, who states that animals often survive even after the escape of large amounts of food from the stomach.

When sealing of the perforation is hindered, as for example by the injection of a substance which produces edema and delays closure, more material is permitted to escape and the mortality in fasted animals rises from 6.9 per cent to 40 per cent.

Openings into the intestine, on the other hand, seal themselves slowly, and early closure is only partially accomplished by a pouting of the mucosa into the defect. This difference between the stomach and the intestine might be explained by the difference in the arrangement of the muscular coats, the muscular tunic of the stomach being both heavier and more intricately arranged than that of the intestine. (Detailed descriptions of the muscular arrangement may be found in textbooks of anatomy.)

The high mortality (100 per cent) following perforations in the terminal ileum is not surprising, because, not only does this region have the most abundant flora of the entire intestinal tract, but the contents are fluid and considerable amounts readily escape when the wall is perforated. Jejunal perforations are less often fatal.

Since the duodenum in fasting animals contains few organisms, the 81.2 per cent mortality following duodenal perforations was a distinct surprise. The most likely explanation is that the duodenal juices which escape into the peritoneal cavity lower the local resistance sufficiently to enable the few organisms present to set up a fatal peritonitis. Blalock[1] has shown that bile and pancreatic juice are injurious to the peritoneum, producing fat necrosis and reddening of the peritoneal surfaces. The local injury probably favors the development of peritonitis. According to Blalock, gastric juice is less harmful than the duodenal juices and our results might be interpreted as confirming his findings.

Paas[11] has made the interesting observation that perforation of the duodenum in dogs induces a temporary reflex spasm of the pylorus which prevents the emptying of the stomach contents into the duodenum. He found that when he closed the perforation within four and a half hours after it had been established the dogs survived. When the perforation was not sutured and the dogs were fed a barium mixture, four of his five dogs died from peritonitis (80 per cent).

Defects in the colon, like those in the small intestine, close slowly, but due to the consistency of the contents of the normal large bowel there is less escape into the peritoneal cavity. Furthermore, the number of viable bacteria in this part of the intestinal tract is less than in most parts of the small intestine.

The mortality following rupture of the gastrointestinal tract as observed by the clinician is governed by the same factors that determine the mortality in experimental perforation. These may be briefly listed as follows:

I. The number and virulence of the escaping organisms
   1. Size of the perforation
   2. Length of time the perforation remains open
   3. Number of organisms at the level of the perforation
      a. Site of the perforation
      b. Length of time after the ingestion of food
   4. Amount and fluidity of material in the viscus at the time of perforation
   5. Forces tending to carrying contents of the viscus out into the peritoneal cavity

II. Resistance of the host
   1. General
   2. Local—may be affected by duodenal juices

It is evident that a large perforation will not only allow the contents of the involved viscus to escape more readily but will also be less likely to seal itself spontaneously.

All surgeons are well aware of the fact that immediate closure of a perforating lesion of the gastrointestinal tract greatly reduces the mortality. Conditions are less favorable for spontaneous closure in clinical cases than in the normal experimental animal. The inflammatory reaction around an ulcer, for example, must definitely retard sealing of the opening. Some indication of this is given in the series of animals in which the injection of a sclerosing solution into the stomach wall preceded the perforation. Clinically, too, we know that perforated ulcers often remain open for long periods. The location of the lesion is also important in determining the time the perforation will remain open. Defects in the normal stomach close almost immediately, probably because of the intricate arrangement of the

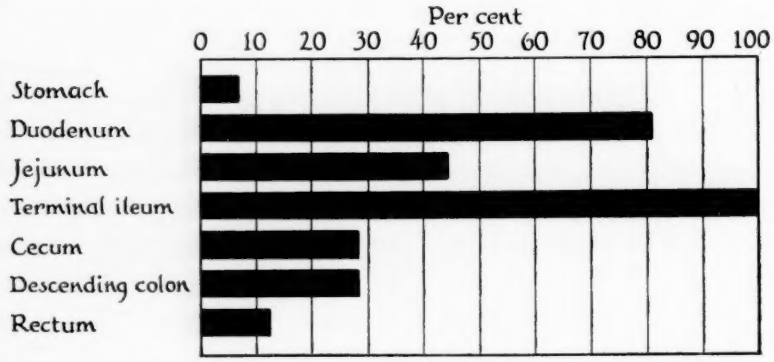

Fig. 4.—Mortality following perforation of the gastrointestinal tract in fasting animals.

muscular tunic. Intestinal perforations, however, gape widely and early but insecure closure is only partially accomplished by a pouting of the mucosa into the defect.

The number of organisms at the level of the perforation depends upon the site of the perforation and the length of time after ingestion of food. Although knowledge of the bacteriology of the intestinal tract is still limited, it is interesting that the mortality curve for our animals (Fig. 4) follows rather closely (except for the high mortality associated with duodenal perforations) the curve of Gilbert and Dominici (Fig. 3).

Clinical evidence supports experimental data. Cushing and Livingood after reviewing their cases of perforating gunshot wounds of the abdomen stated that "recovery had followed in those cases alone in which the perforations had been situated at no great distance from the pyloric end of the intestine, whereas all of the cases in our particular series in which the perforations had been far down in the

ileum had succumbed to an ensuing peritonitis, though many of them had been operated upon at a comparatively early period and favorable prognoses had been given.''

Further evidence has been supplied by cases of accidental perforation of the empty stomach during examination with the flexible gastroscope. Five such cases have been reported in the literature[12] and one occurred in our own clinic. All of these six cases recovered without ill effects. The case from our clinic showed pneumoperitoneum on x-ray examination but failed to develop any signs of peritonitis and recovered completely without operation.

The amount and fluidity of material in the viscus affect the mortality by influencing the ease with which material escapes through the perforation.

Traumatic rupture of the intestinal tract almost always results in great contamination of the peritoneal cavity, because the injuring force

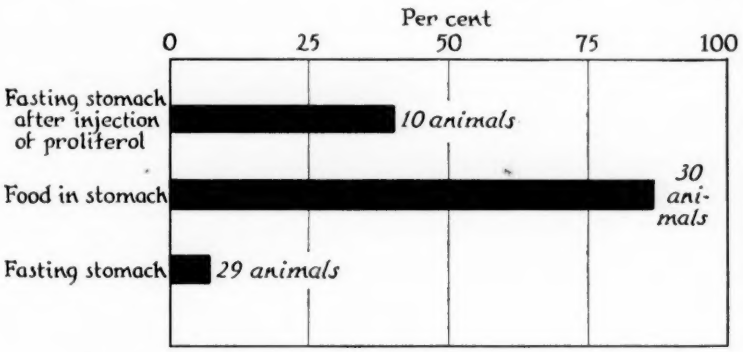

Fig. 5.—Mortality following perforations of the stomach.

carries intestinal contents out into the peritoneal cavity. A striking example of this is the compressed air rupture of the pelvic colon.[10] The outlook in such cases is distinctly unfavorable because of the widespread peritoneal contamination.

The other factors, the local and general resistance of the host, influence the mortality in clinical cases just as they do in the experimental animal.

These observations emphasize the importance of therapeutic measures directed at early closure of the perforation. Furthermore, in lesions involving the stomach or duodenum, evacuation of the contents of the viscus should be accomplished and maintained by continuous suction.[13] Even as late as the beginning of the World War (1914-1918) some well-recognized surgeons on both sides engaged in the conflict advocated conservative therapy for perforating gunshot wounds of the abdomen.[4, 9] Anyone who still doubts the validity of operation in cases of penetration

of the gastrointestinal canal by missiles from firearms should read the illuminating report of Enderlen and Sauerbruch[4] in which the superiority of the immediate operative attack is unequivocally shown.

SUMMARY

1. The factors influencing the mortality following perforation of the gastrointestinal tract have been enumerated.

2. Experimental perforations have been established at different levels in animals and the results tabulated.

3. The mortality following perforation of the empty stomach was 6.9 per cent, but when the stomach contained food the mortality rose to 86.7 per cent. Injection of a sclerosing solution into the stomach wall before perforation increased the mortality in fasting animals to 40 per cent.

4. In the small intestine the mortality was 81.2 per cent following duodenal perforation, 44.4 per cent following jejunal perforation, and 100 per cent following perforation of the terminal ileum.

5. The mortality following perforation of the large bowel was 23.1 per cent.

REFERENCES

1. Blalock, A.: Experimental Studies on the Effects of the Perforation of Peptic Ulcers, Surg., Gynec. & Obst. **61**: 20, 1935.
2. Borman, C. N., and Bergh, G. S.: Unpublished data.
3. Cushing, H., and Livingood, L. E.: Experimental and Surgical Notes Upon the Bacteriology of the Upper Portion of the Alimentary Canal, With Observations on the Establishment There of an Amicrobic State as a Preliminary to Operative Procedures on the Stomach and Small Intestine, Johns Hopkins Hosp. Rep., Balt. **9**: 543, 1900.
4. Enderlen, E., and Sauerbruch, F.: Die operative Behandlung der Darmschüsse im Krieg, Med. Klin. **11**: 823, 1915.
5. Gilbert, A., and Dominici, S. A.: Recherches sur le nombre des microbes du tube digestif, Compt. rend. Soc. de biol. **46**: 117, 1894.
6. Himmelmann, W.: Tierexperimentelle Untersuchungen über die Folgen der Magenperforation nach Röntgenkontrastmahlzeit, Deutsche Ztschr. f. Chir. **240**: 62, 1933.
7. Himmelmann, W.: Tierexperimentelle Untersuchungen über die Folgen der Magenperforation nach Röntgenmahlzeit: Verlauf und Ausgang der Perforation des mit Bolus alba gefüllten Magens, Deutsche Ztschr. f. Chir. **246**: 53, 1935.
8. Kendall, A. I.: Recent Developments in Intestinal Bacteriology, Am. J. M. Sc. **156**: 157, 1918.
9. Lockhart-Mummery, P.: Injuries to the Bowel From Shell and Bullet Wounds, Brit. M. J. **2**: 914, 1914.
10. McGlannon, A.: Colon, Dean Lewis Practice of Surgery, vol. 7, chap. 4, p. 13. Hagerstown, 1931, W. F. Prior Company, Inc.
11. Paas, H. R.: Über die Magen- und Duodenalperforation nach Röntgen-Kontrast-mahlzeit und ihre Folgen, Deutsche Ztschr. f. Chir. **247**: 461, 1936.
12. Schindler, R., and Renshaw, J. F.: Experimental Study With Certain Tips Used on the Wolf-Schindler Flexible Gastroscope, Am. J. Digest. Dis. & Nutrition **3**: 747, 1936.
13. Wangensteen, O. H.: Nonoperative Treatment of Localized Perforations of the Duodenum, Minnesota Med. **18**: 477, 1935.
14. Wangensteen, O. H.: Abdominal Injuries, Internat. S. Digest. **21**: 323, 1936.

PRIMARY CARCINOMAS OF THE STOMACH AND SIGMOID FLEXURE OCCURRING SIMULTANEOUSLY IN THE SAME INDIVIDUAL

JOHN DEJ. PEMBERTON, M.D., AND JOHN M. WAUGH, M.D.,
ROCHESTER, MINN.
(From the Mayo Clinic)

MULTIPLE primary carcinomas which affect the same individual have aroused the interest of the profession since the first reports of such lesions in 1869 by Billroth, although the frequency with which present-day pathologists report this finding is tending to make it almost commonplace. However, the finding clinically of two separate and distinct carcinomas appearing simultaneously in the sigmoid flexure and stomach is rare, and this, coupled with the fact that both lesions were amenable to surgical treatment, makes the report of the following case unique.

REPORT OF CASE

A male physician, aged fifty-seven years, came to the Mayo Clinic, August 17, 1935, complaining of constipation which had been present for three months and attacks of intestinal obstruction. About three weeks prior to his admission, he had had his first severe episode of obstruction, which had been associated with nausea, distention, and cramps. The attack had been relieved in about four days by enemas and pitressin. A barium enema revealed an obstruction in the sigmoid flexure. After a barium meal had been given, the patient had another similar severe episode of obstruction and was rushed by plane to the clinic. He had lost 15 pounds (6.8 kg.) in two months. Examination at the clinic revealed that the acute intestinal obstruction had subsided; the abdomen was flat, soft, and not tender. There was a visible and palpable mass in the region of the sigmoid flexure. This mass was about 4½ inches by 2 inches (11.43 cm. by 5 cm.); it was firm, nodular, and freely movable. Except for a chronic "cigaret" cough, he had no other complaints.

His past history revealed that he had had osteomyelitis of the right mandible in 1934, and an appendectomy had been performed in 1900. Urinalysis and examinations of the blood did not reveal any abnormality. Roentgenoscopic examination of the colon with a barium enema revealed a carcinoma of the sigmoid flexure at the junction of the sigmoid flexure and the descending colon. Proctoscopic examination of the rectum and sigmoid flexure did not reveal any abnormality except hemorrhoids.

The clinical diagnosis was carcinoma of the proximal portion of the sigmoid flexure. Exploration of the tumor was undertaken by one of us (J. deJ. P.), August 22, 1935, using spinal anesthesia. Preliminary exploration of the upper part of the abdomen for metastasis disclosed a tumor about the size of the fist which involved the distal third of the stomach. This tumor was firm and had sharp nodular edges. It was believed to be another primary malignant tumor

Received for publication, January 12, 1937.

which should be removed at a later date. There was no evidence of metastasis from either tumor. The carcinoma in the sigmoid flexure had perforated onto the lateral wall of the peritoneum but was definitely operable, so the portion of bowel about and including the tumor was brought outside as the first stage of the Mikulicz operation. The second stage of the operation, which was performed August 31, 1935, included removal of the growth with cautery. The pathologic report was adenocarcinoma, grade 2, of the sigmoid flexure without involvement of the lymph nodes. A clamp was applied to the colonic spur at the Mikulicz stoma.

At this time, clinical examination of the lesion in the stomach was undertaken. Roentgenoscopic examination with the barium meal showed a large ulcerating carcinoma of the pyloric end of the stomach with perforation; the lesion appeared to be operable locally. Aspiration of the gastric contents did not reveal any free hydrochloric acid. The value for the total acidity ranged from 10 to 16 according to the method of Töpfer.

Subtotal resection of the stomach was undertaken on September 19, 1935, by one of us (J. deJ. P.), using ethylene anesthesia. The approach was through an upper midline incision. The growth was freely movable in the pyloric end of the stomach and formed a mass which was the size of a doubled fist. There was no metastasis. A resection of the pyloric two-thirds of the stomach was done by turning in the end of the duodenum and making an anterior Polya type of anastomosis with an entero-anastomosis between the proximal and distal limbs of the jejunum. A small tumor about 1 cm. in diameter which was found in the upper part of the jejunum was removed. Microscopically it proved to be a neurofibroma. The lesion in the stomach was found to be an ulcerating adenocarcinoma, grade 2. There was no involvement of the lymph nodes.

The convalescence was very satisfactory, and after the application of clamps to the colonic spur, the opening in the colon at the site of the Mikulicz operation was closed, and when the patient was discharged, January 13, 1936, both wounds were well healed.

When he returned to the clinic, August 18, 1936, for reexamination, he said that he had been feeling very well and had been working daily. Careful physical examination, as well as roentgenologic examination of the thorax, colon, and stomach, failed to reveal the slightest evidence of recurrence or metastasis.

Although the patient was a physician, he insisted that he never had had the slightest symptom referable to his stomach or epigastrium. He always had been able to eat or drink with impunity. This is of interest because of the large size of the growth in the stomach, its ulceration and position at the outlet, all of which should have made the lesion prone to produce symptoms. It was very gratifying to all concerned that after a year no recurrence of either lesion was demonstrable by careful roentgenoscopy.

COMMENT

Warren and Gates, in an encyclopedic review of the literature in 1932, found 1,259 reported cases of multiple malignancy which they believed authentic, including their own cases. Practically all of these lesions were found at necropsy. These authors, as well as Hanlon, rightfully found Billroth's original criteria for the diagnosis of multiple primary malignancy too strict and substituted the following rules: (1) Each of the tumors must present a definite picture of malignancy; (2) each must be distinct; and (3) the probability of one's being a metastasis of the other must be excluded.

Hanlon, in reviewing 3,000 necropsies at the clinic, found 710 cases of malignancy, among which there were eighteen instances of multiple primary carcinomas. In these latter cases, the colon was involved nine times and the stomach three. In only two cases were the multiple growths recognized clinically. About half of the tumors were "silent" and did not give rise to any symptoms. Hurt and Broders, in an analysis of 2,124 cases in which microscopic examination revealed the presence of carcinoma, found that seventy-one of the patients previously had had carcinoma. They estimated that in 4 per cent of the cases in which a carcinoma is found, the patients have or will have later another independent carcinoma. In their series of 152 distinct lesions, the colon was affected in nine cases and the stomach in only one case. Hurt and Broders concluded that "multiple primary malignant neoplasms occur most commonly in the same organ or in organs of the same system. From the study of cases of multiple malignant neoplasms, it seems that the factors which cause the development of the tumors also express themselves in the grade of malignancy of the tumors." This latter fact is well borne out by the two lesions in the case reported, both of which were grade 2.

Warren and Gates, in their review of the literature prior to 1932, found the colon and stomach to be involved with simultaneous independent carcinomas in thirty of 1,259 cases of multiple primary carcinomas which they collected. In only three of these thirty cases was it definitely stated that the sigmoid flexure was affected.

Since this publication in 1932, there have been four more reported instances of multiple primary carcinomas in the colon and stomach; in none of these cases was the sigmoid flexure involved and in only one case did the carcinomas appear simultaneously. These four cases were reported by the following authors: Cecil Joll, in 1932, reported the resection, in 1930, of a lymphosarcoma of the stomach in a case in which he had performed a combined abdominoperineal resection in 1928 for carcinoma of the rectum. E. S. Judd and J. R. Phillips, in 1934, reported the resection of a carcinoma of the rectum six and a half years after the removal of a carcinomatous gastric ulcer. M. P. Bull, in 1932, reported the interesting finding of multiple primary carcinomas involving the colon and stomach of two brothers. In one case, the transverse colon was simultaneously involved with the stomach; in the other case, the growth appeared in the right half of the colon subsequent to resection of the stomach. All four tumors were successfully removed surgically.

These four, with our case, make a total of thirty-five reported instances of independent carcinomas which involved the colon and stomach. In only four of these cases was the sigmoid flexure involved.

The case herein cited is, so far as we are aware, the only recorded instance of successful surgical removal of simultaneous independent carcinomas of the stomach and sigmoid flexure.

REFERENCES

1. Billroth, C. A. T.: Quoted by Shields Warren, and Olive Gates.
2. Bull, M. P.: Sur deux cas de cancer du côlon et de l'estomac observés sur deux frères, Bull. et mém. Soc. nat. d. chir. **58**: 1338-1343, 1932.
3. Hanlon, F. R.: Multiple Primary Carcinomas, Am. J. Cancer (Suppl.) **15**: 2001-2012, 1931.
4. Hurt, H. H., and Broders, A. C.: Multiple Primary Malignant Neoplasms, J. Lab. & Clin. Med. **18**: 765-777, 1933.
5. Joll, Cecil: Multiple Primary Malignant Growths in the Same Patient, Tr. M. Soc., London **55**: 45-47, 1932.
6. Judd, E. S., and Phillips, J. R.: Independent Carcinoma of the Colon Occurring Six Years After Carcinoma of the Stomach, S. Clin. North America **14**: 525-528, 1934.
7. Warren, Shields, and Gates, Olive: Multiple Primary Malignant Tumors: A Survey of the Literature and a Statistical Study, Am. J. Cancer **16**: 1358-1414, 1932.

ACUTE APPENDICITIS: A STUDY OF ONE THOUSAND CONSECUTIVE PATIENTS

JAMES A. KIRTLEY, JR., M.D., AND ROLLIN A. DANIEL, JR., M.D.,
NASHVILLE, TENN.

(From the Department of Surgery, Vanderbilt University School of Medicine)

THIS report is based on the cases of acute appendicitis admitted to the Vanderbilt University Hospital during a period of approximately 10 years. The majority of the patients have come from rural districts, many of them from distances of 100 miles or more. The series includes private patients, but these compose only about 15 per cent of the entire group. The instances in which the appendix was removed during the course of an operation for some other condition are not included, nor are those cases in which the diagnosis was not substantiated by either operation or autopsy.

The study was undertaken to determine the mortality of the entire group, the mortality of the group in which the appendix was ruptured, and, if possible, to determine the factors which influenced the mortality in the latter group.

All patients are sent from the admitting office to the wards and never directly to the operating room. Those patients who have peritonitis are seen by the resident surgeon and by a senior staff surgeon. If the patient is dehydrated, regardless of the stage of the inflammatory process, operation is deferred for a time sufficient to administer fluids. Should further delay be thought advisable, the patient is given nothing by mouth; fluids are administered subcutaneously; and morphine is given at frequent intervals.

Postoperatively these same measures are usually employed. Frequent small blood transfusions are given in many cases in which the appendix is ruptured, and are believed to be of definite value. Vomiting is combatted by the use of duodenal suction siphonage.

Most of the operations are performed by the resident surgeon, usually in the fourth or fifth year of his surgical training, and a comparison of each surgeon's mortality rate shows very little variation. McBurney's incision has been used in relatively few instances, the Battle-Kammerer incision being used in most of the operations. The appendix has been found in most instances to be easily accessible with this approach. Most of the operations have been performed under general anesthesia, local anesthesia being used only when nitrous oxide and ether were thought to be definitely contraindicated. No definite routine is observed regard-

Received for publication, February 6, 1937.

ing delay in operation on patients with peritonitis. This point will be considered later. Where removal of the appendix in the presence of peritonitis necessitates a long anesthetic or much manipulation, drainage without an attempt to remove the appendix has generally been practiced.

The series is divided into two main groups; viz., the patients in whom the appendix was not ruptured, and those in whom the appendix was ruptured. The latter group is subdivided as follows:

Appendiceal Abscess.—Those patients in whom the inflammatory process is well walled off around or near the appendix.

Localized Peritonitis.—The cases in which the inflammatory process is still confined to the region of the appendix and has not been walled off to form an abscess.

Spreading or Generalized Peritonitis.—The cases in which the inflammatory process has spread to involve a large portion of the peritoneal cavity without evidence of localization.

TABLE I

MORTALITY RATES IN FIVE-YEAR AGE GROUPS

AGE LIMITS	NUMBER OF CASES ACUTE APPENDICITIS	RUPTURED APPENDICITIS	TOTAL NUMBER OF CASES	NUMBER OF DEATHS (TOTAL)	MORTALITY (TOTAL) PER CENT
0-5	4	9	13	3	23.0
6-10	31	36	67	6	9.0
11-15	100	59	159	10	6.3
16-20	182	54	236	8	3.4
21-25	159	33	192	4	2.1
26-30	88	28	116	6	5.2
31-35	40	23	63	4	6.3
36-40	33	16	49	2	4.8
41-45	17	20	37	6	16.2
46-50	14	14	28	2	7.1
51-55	7	9	16	2	12.5
56-60	5	5	10	1	10.0
61-65	2	5	7	2	28.5
66-70	0	4	4	1	25.0
71-75	0	1	1	0	0

In the 1,000 cases, there were 57 deaths, but 6 of the patients who died were not operated upon, for reasons which will be given in detail later. The mortality rate in the 994 cases operated upon was 5.1 per cent.

Color.—There were 876 white and 124 colored patients. In 252 of the white patients, or 28.8 per cent, the appendix was ruptured, and there were 45 deaths, the mortality rate being 5.1 per cent. In the group of colored patients, 64, or 51.6 per cent, had ruptured appendices, and the mortality rate was 9.7 per cent, there being 12 deaths.

Sex.—The incidence of appendicitis was predominant in males. Of the 587 male patients, 215, or 36.9 per cent, had ruptured appendices; 38 of these patients died, a mortality rate of 6.5 per cent. In the 413 female patients, the appendix was ruptured in 99, or 23.9 per cent, and there were 19 deaths, a mortality rate of 4.6 per cent.

Age.—In Table I, all cases are divided into 5-year age groups. The mortality rate is seen to be considerably higher in patients below the age of 10 years and above the age of 50 years than in the groups between these limits and is lowest in the period between the ages of 15 years and 25 years. The incidence of the disease is the inverse of this, being highest in the 15-year to 25-year group and lowest in the extremes of life. It is also interesting to note that the proportion of ruptured to unruptured appendicitis is higher in the vary young and very old.

Mortality Rate for Each Year.—This is shown in Table II. There were no deaths in 1925 or in 1928, although in one-third of the cases in

TABLE II

MORTALITY RATE FOR EACH YEAR

YEAR	TOTAL NUMBER CASES	NUMBER OF DEATHS	MORTALITY PER CENT
1925	15	0	0
1926	42	3	7.1
1927	38	2	5.2
1928	66	0	0
1929	73	3	4.1
1930	87	5 (1 acute)	5.7
1931	138	7	5.1
1932	155	11	7.1
1933	149	6	4.0
1934	113	14	12.4
1935	124	7	5.6

1925 and in one-fourth of the cases in 1928, the appendix was ruptured. In 1934, there was a relatively large number of patients who were moribund at the time of admission. With the exception of the high mortality during this year, there is no definite trend toward a higher or a lower mortality in this series over the period of ten years. In Table III, the incidence of ruptured appendicitis is given for each year. It is interesting to note that there is an almost unbroken decrease in the ratio

TABLE III

PERCENTAGE RUPTURED APPENDICES AT TIME OF OPERATION
RATIO RUPTURED TO TOTAL NUMBER OF CASES DURING EACH YEAR

YEAR	NUMBER PATIENTS WITH UNRUPTURED APPENDICES	NUMBER OF PATIENTS WITH RUPTURED APPENDICES	TOTAL	CASES RUPTURED AT OPERATION PER CENT
1925	10	5	15	33.3
1926	23	19	42	45.0
1927	24	14	38	36.8
1928	51	15	66	22.7
1929	56	17	73	23.3
1930	69	18	87	20.6
1931	99	39	138	28.2
1932	116	39	155	25.1
1933	98	51	149	34.2
1934	65	48	113	42.5
1935	74	50	124	40.3

of ruptured cases to the total number until the time of the recent economic depression, the incidence being 45 per cent in 1926 and 20.6 per cent in 1930. The ratio then became greater in each succeeding year until in 1934 it was 42.5 per cent, dropping back to 40.3 per cent in 1935.

Duration of Symptoms.—In Table IV, all cases operated upon are grouped according to the duration of the patients' symptoms, and the

TABLE IV

DURATION OF SYMPTOMS AND MORTALITY RATE

DURATION OF SYMPTOMS AT TIME OF OPERATION	NUMBER OF CASES	NUMBER OF DEATHS	MORTALITY RATE PER CENT
0 to 24 hours	342	4	1.2
24 to 48 hours	247	11	4.5
48 to 72 hours	111	12	10.9
4th day	57	6	10.5
5th day	39	4	10.2
6th day	33	4	12.1
7th day	37	4	10.7
8th to 14th day	68	5	7.3
Over 14 days	60	1	1.7

mortality rate is shown for each group. As would be expected, the mortality is lowest in the patients operated upon during the first twenty-four hours. It is highest in the group operated upon during the sixth day, the mortality varying little in the five groups between the third and seventh days, inclusive. These groups include most of the patients with generalized peritonitis and all of the patients who were moribund at the time of admission.

There were 686 patients in whom the appendix was not ruptured, and 314 in whom the appendix was ruptured. Thus, 31.4 per cent of the total number of patients had ruptured appendices at the time of admission.

UNRUPTURED APPENDICES

In the group in which the appendix was not ruptured, there was only one death, a colored female of twenty-five years of age, who died three days after operation. Autopsy was limited to exploration of the wound at the undertaking parlor. There was no evidence of hemorrhage, infection, or intestinal obstruction. Clinically, the death was thought to be due to massive pulmonary collapse. This is a mortality rate of 0.145 per cent in this group.

The following surgical pathologic diagnoses were made:

Acute appendicitis	494 cases
Subacute appendicitis	84 cases
Chronic obliterating appendicitis	39 cases
No microscopic lesion	69 cases

Of the 69 appendices in which there was no gross or microscopic evidence of inflammation, 13 were removed as "interval appendec-

tomies'' because of the history of repeated attacks of right lower quadrant pain. Sixteen had abdominal pain at the time of admission, but operation was delayed from twelve hours to four days after admission. These patients were carefully studied and operation advised because of previous attacks. In the remaining 40 patients, the operation was performed immediately, but in 9 of these, other conditions, such as urinary infection, were recognized before operation. In 31 cases out of the 1,000, there was no history of previous attacks. Operation was performed immediately and a normal appendix removed, and nothing else was found to account for the patient's symptoms.

RUPTURED APPENDICES

The 314 patients with ruptured appendices were the ones most carefully studied. There were 56 deaths in this group, but 6 patients not operated upon are excluded, leaving 50 deaths, a mortality rate of 16.3 per cent for all cases of ruptured appendicitis in which operation was performed.

In Table V, the entire series is divided into the four groups as previously outlined, and the mortality rate for each group is shown.

TABLE V

CLASSIFICATION ACCORDING TO THE STAGE OF THE DISEASE—MORTALITY RATES

	NUMBER OF CASES	NUMBER OF DEATHS	MORTALITY PER CENT
Acute appendicitis	686	1	0.145
Appendiceal abscess	118	5	4.2
Localized peritonitis	87	7	8.1
Spreading or generalized peritonitis	103	38	36.9

Appendiceal Abscess.—There were 118 patients with appendiceal abscess, 5 of whom died, mortality rate of 4.2 per cent. In this group, operation was performed immediately in 63 cases and was delayed in 55. All of the 5 deaths are included in the group of 55 in which operation was delayed. The appendix was removed at the time of the first operation in 79 cases; and in 39 cases, the abscess was drained without an attempt to remove the appendix. Four of the deaths were in the latter group; 1 dying of lobar pneumonia, and another dying of a pulmonary embolus, both having had satisfactory courses before onset of the complication. The 3 remaining patients died of generalized peritonitis.

Localized Peritonitis.—There were 87 cases of localized peritonitis with 7 deaths, a mortality rate of 8.1 per cent. Operation was performed immediately upon all of these patients, and the appendix removed in all cases except 1, the patient making an uneventful recovery in this one

instance. Five of the deaths were due to generalized peritonitis, the other 2 dying of extensive bronchopneumonia, the diagnosis being verified by portable roentgenograms.

Spreading or Generalized Peritonitis.—There were 103 patients in this group with 38 deaths, a mortality rate of 36.9 per cent. Operation was deferred in 25 cases, and 8 of these patients died, the mortality rate for this "deferred group" being 32 per cent. Seventy-eight patients were operated upon immediately, 30 of them dying, the mortality rate being 38.5 per cent. Of the 103 cases, the appendix was removed in 84, drainage alone being instituted in 19. There were 13 deaths in the small group in which the appendix was not removed. This is accounted for, in part, by the fact that out of 7 patients who were moribund or nearly so at the time of operation, the appendix was not removed in 5 cases, drains being inserted in the right iliac fossa under local anesthesia and the operation requiring only a few minutes' time.

Of the 258 cases of ruptured appendicitis which recovered, 132, or 51.2 per cent, had purgatives before admission. In the group of 50 deaths, 68 per cent had purgatives.

ANALYSIS OF DEATHS

At the time of operation, 38 out of the 50 of those who died had an unmistakable generalized peritonitis. Seven of these patients, as was noted previously, were moribund or nearly so. The anesthetist's records show that 6 of the patients who died had operation under novocaine anesthesia alone, and in 5 others, novocaine was supplemented by nitrous oxide. Six had nitrous oxide alone, and 33 had gas induction and ether anesthesia.

In 22 cases, the operation was completed in less than thirty minutes, the seven patients who were nearly moribund being included in this group. In the remaining 28 cases operation required from thirty to one hundred minutes, with an average of fifty-five minutes. This includes the entire time that the patient was on the table, the anesthetic being discontinued as soon as the peritoneum was closed.

The reasons for not operating on the 6 patients who were excluded are as follows:

Two of the patients were moribund on admission, both expiring about seven hours after they were admitted. One of them was a man sixty-five years old. Two others lived four and one-half and six days after admission. One had been sick seven days, the other three days, and both had generalized peritonitis. They showed signs of improvement with conservative treatment, but both became suddenly worse a few hours before death, quickly became moribund, and both died with generalized peritonitis.

The fifth patient was a twelve-year-old white girl who had been sick six days before admission, having had fever, chills, but no abdominal

pain or other symptoms suggesting appendicitis. On admission the abdomen was soft, and there was no evidence of localized intraperitoneal infection. She continued to have fever, and eight days after admission began again to have frequent chills. Careful study failed to reveal any cause for her fever. Twenty-four hours before death, which occurred on the sixteenth day, the abdomen became distended, and she developed unmistakable evidence of generalized peritonitis. Autopsy revealed a gangrenous perforated appendix, a rather early generalized peritonitis, septic thrombosis of the portal veins, and multiple liver abscesses.

The sixth patient was a four-year-old boy who had hydrocephalus. Two craniotomies were performed, an ependymablastoma obstructing the iter being partially removed at the second operation. Following this, he remained comatose, and his condition grew gradually worse with high daily temperature elevations and, after several days, with marked abdominal distention and signs of general peritonitis without any evidence of localization. At autopsy a gangrenous appendix and generalized peritonitis were found.

Autopsy was obtained in 37 cases and the following conditions were found:

Generalized peritonitis	35 cases
Bronchopneumonia	17 cases
Volvulus of ileum	4 cases
Subdiaphragmatic abscess	4 cases
Pylephlebitis and liver abscess	3 cases
Streptococcus septicemia	4 cases
Fecal fistula	1 case

In the 13 cases in which autopsy was not obtained, 11 patients had unmistakable evidence of generalized peritonitis before death. In one of the other cases, the patient had extensive lobar pneumonia and died on the tenth postoperative day. The other patient died on the eighth day, probably of a pulmonary embolus.

The 6 patients who were not operated upon were all found at autopsy to have generalized peritonitis. The single death in the series of cases in which the appendix was not ruptured was due to massive pulmonary collapse.

The causes of death were:

Generalized peritonitis	52 patients
Bronchopneumonia	2 patients
Lobar pneumonia	1 patient
Pulmonary embolus	1 patient
Massive pulmonary collapse	1 patient

DISCUSSION

A brief comparison of mortality rates in appendicitis recently reported by several other university hospitals is shown in Table VI.

The average of these figures for each group is given and a careful study shows that the mortality rates of each clinic vary little and are near the average figures for the entire group. There is basically little difference in the methods of treatment employed in these institutions. Pattison,[1] of the University of Iowa, found the mortality rate to be higher in the cases in which a right rectus incision was made than in those in which the McBurney incision was used, but he stated that this is suggestive and not conclusive evidence of the relative value of the two incisions. In 1934, Reid[2] reported 409 cases of acute appendicitis operated upon at Cincinnati General Hospital between the years 1915 and 1922, the right rectus incision being used routinely and the mortality rate being 9.8 per cent. In 1922, the McBurney incision was adopted and has been used exclusively from 1922 to 1934 in 1,626

TABLE VI

COMPARISON OF MORTALITY STATISTICS IN UNIVERSITY HOSPITALS

	*UNIVERSITY OF MINNESOTA (SPERLING, L.[6]) 1932-1934		UNIVERSITY OF MICHIGAN (COLLER AND POTTER) 1931-1933		UNIVERSITY OF IOWA (PATTISON) 1919-1934		VANDERBILT UNIVERSITY 1925-1935		AVERAGE MORTALITY
	NO. OF CASES	MORTALITY	NO. OF CASES	MORTALITY	NO. OF CASES	MORTALITY	NO. OF CASES	MORTALITY	
Simple acute appendicitis	110	0.99%	213	0.46%	814	0.37%	686	0.15%	0.49%
Appendiceal abscess	59	6.7%	35	5.7%	268	8.6%	118	4.2%	6.3%
Local peritonitis	21	9.5%	88	12.5%	48	4.2%	87	8.1%	7.7%
General peritonitis	46	43.4%			81	43.2%	103	36.9%	41.2%
Total	236	7.5%	336	4.1%	1211	5.2%	994	5.1%	5.5%

*Since this paper was sent to the publishers, a more complete group of cases from the University of Minnesota by Sperling, L., and Myrick, J. C., has appeared in SURGERY 1: 255, 1937.

patients with acute appendicitis. The mortality rate for this period was 5.2 per cent. It seems possible that other changes in operative technic, as well as in the care of the patient preoperatively and postoperatively, may have contributed largely to this reduction in mortality rate. Keyes,[3] in 1934, reported 1,859 cases of appendicitis in the Barnes and St. Louis Children's Hospital with a mortality rate of 3.33 per cent; the right rectus incision had been used more frequently in that clinic. In our series of cases, the mortality rate for those operated upon is 5.1 per cent; the McBurney incision has been used infrequently except where drainage of an appendiceal abscess is instituted. The technical difficulties encountered in using the Battle-Kammerer incision are not great if the incision is not very long, if it is placed near the lateral border of the rectus muscle, and if one exercises the proper care in packing off the surrounding loops of intestine before removing the

appendix. If local anesthesia is used, the appendix can be removed with greater ease through a McBurney incision. There is actually so little difference between these two incisions that the advantages of each are probably overemphasized, and the improvements in the care of the patient, the importance of fluids and blood transfusions, and the wider choice of anesthetics are the factors which have lowered the mortality rate in the most recent series.

Coller and Potter[4] give an excellent discussion of the so-called "delayed" treatment of patients with ruptured appendicitis. They advocate delay of operation until the inflammatory process has become well walled off. In general, we feel that delay in operation is justified when there is no doubt that the appendix is ruptured and that the peritonitis is not spreading or that the patient's general condition may be greatly improved by delay. If the patient is markedly dehydrated, every attempt should be made to correct this before subjecting the patient to operation. The fact that the appendix is not ruptured in occasional cases in which a preoperative diagnosis of early ruptured appendicitis with localized peritonitis is made, justifies immediate operation on all of these patients.

There is complete agreement as to the value of immediate operation in all cases of unruptured appendicitis, but a wide difference of opinion exists as regards the proper treatment of patients with early generalized peritonitis who have been sick from three to five days. Many surgeons advocate immediate removal of the appendix with drainage, and as many more counsel delay of operation until an abscess forms, usually from ten to fourteen days after onset. We believe that each of these patients must be considered individually and if delay of operation is decided upon, then fluids subcutaneously and morphia in sufficient amounts should be given, but we always reserve the right of intervening if the patient does not seem to respond to conservative measures. We have not infrequently seen patients who had had generalized peritonitis for three or four days show improvement after complete rest and fluids for several days, and then on the sixth, seventh, or eighth day of peritonitis again have increased fever, rapid pulse, and vomiting. With drainage at this point, many of these patients show immediate improvement.

Drainage of the right iliac fossa and of the pelvis when the appendix is ruptured and free pus is present is deemed the wisest procedure in spite of the possibility of fecal fistula or intestinal obstruction later. These complications have been infrequent in this clinic. In an occasional patient with ruptured appendicitis the wound has been closed without drainage.

The persistent catharsis by the patient and family, and, more important, the late hospitalization of patients with appendicitis are still the factors that more than any others should be corrected. The results of

lay instruction are shown in Philadelphia, which has one of the lowest death rates of any city in the country and which has employed the best system of education of the laity.[5]

SUMMARY

1. A study of 1,000 consecutive patients in whom a diagnosis of acute appendicitis was made is presented. These patients were admitted to the Vanderbilt University Hospital between the years 1925 and 1935, inclusive.

2. The mortality rate for the entire group is 5.1 per cent, 6 patients who were not operated upon being excluded.

3. Of the 686 cases of unruptured acute appendicitis, there was 1 death, a mortality rate of 0.145 per cent.

4. Of the 308 cases of ruptured appendicitis in which operation was performed, there were 50 deaths, a mortality rate of 16.3 per cent.

5. The mortality rate and incidence of ruptured appendicitis are highest at the two extremes of life.

6. In approximately 1 case in every 3, the appendix was ruptured at the time of admission.

7. In more than half of the cases of ruptured appendicitis, the patients had received catharsis before admission.

8. Our own results agree closely with those recently reported by similar institutions.

9. The importance of considering each case individually and reserving the right to intervene in those cases in which delay is at first decided upon, is emphasized.

10. Instruction of the laity in the symptoms of acute appendicitis and in the value of early operation in these cases offers the best chance for reduction of the present mortality rate.

REFERENCES

1. Pattison, Arthur C.: Factors in the Mortality of Acute Appendicitis, Ann. Surg. **103**: 362, 1936.
2. Reid, Mont R.: Some Remarks on Operative Procedures for Appendicitis, Surg., Gynec. & Obst. **59**: 529, 1934.
3. Keyes, E. Lawrence: Death From Appendicitis, Ann. Surg. **99**: 47, 1934.
4. Coller, F. A., and Potter, E. B.: The Treatment of Peritonitis Associated With Appendicitis, J. A. M. A. **103**: 1753, 1934.
5. Bower, J. O.: Appendicitis in Philadelphia, J. A. M. A. **102**: 813, 1934.
6. The University of Minnesota Hospital Bulletin, Vol. 6, No. 8, Nov. 15, 1934.

FUNDAMENTAL PRINCIPLES IN THE TREATMENT OF DIABETIC GANGRENE

SAUL S. SAMUELS, M.D., NEW YORK, N. Y.

(From the Clinic for Peripheral Arterial Diseases and the Fourth Surgical Division, Bellevue Hospital, and the Department of Arterial Diseases, Stuyvesant Polyclinic Hospital)

PROLONGATION of the life of the diabetic through the use of insulin has created an alarming increase in the occurrence of arteriosclerotic disease. Aside from the visceral manifestations of arteriosclerosis, such as coronary artery narrowing or thrombosis, the peripheral, arterial disturbances now seen so frequently in diabetic patients are worthy of serious consideration and study.

To avoid confusion, it is advisable to clarify the terminology of arteriosclerosis of the peripheral vessels, keeping in mind the underlying pathologic changes involved. In general, it may be stated that from the clinical standpoint the term arteriosclerosis has replaced the less commonly used atherosclerosis and endarteritis. When the arteriosclerotic process is combined with an obliteration of the arterial lumen either by narrowing or by thrombosis, it is qualified by adding the adjective obliterans. In other words, one may speak of arteriosclerosis of the peripheral arteries minus interference with blood flow. When, however, evidence of obstructed flow is also present, the condition should rather be described as one of arteriosclerosis obliterans, which is the preferred modern designation. In this connection it is important to note that extensive calcification of arteriosclerotic arteries may be visible on roentgen examination with, however, no evidence of impaired circulation resulting therefrom. This condition is properly described as arteriosclerosis with calcified arteries. When, however, there are also clinical signs or symptoms suggestive of impairment of the arterial onflow, the correct terminology is arteriosclerosis obliterans with calcification. If diabetes mellitus is also present, the proper designation is diabetic arteriosclerosis obliterans. With the appearance of gangrene, one speaks of either arteriosclerotic gangrene or diabetic arteriosclerotic gangrene. Since, however, almost every case of gangrene of the extremities in a diabetic is primarily of arteriosclerotic origin, it is simpler to employ the widely used designation diabetic gangrene in everyday parlance.

Another advantage in the use of the term arteriosclerosis obliterans is the clear distinction from the other important obliterating disease of the peripheral vessels, thromboangiitis obliterans.

Received for publication, February 25, 1937.

CLASSIFICATION

The onset of gangrene in the arteriosclerotic extremity may be precipitated by the gradual narrowing of the arterial channels or by sudden occlusion due to thrombosis. In the former group, the narrowing has usually progressed slowly enough over a long period of time to allow for the spontaneous formation of collateral circulation, sparse though it is in arteriosclerosis; whereas in the sudden occlusive type, there is hardly any time for the establishment of collateral circulation. (Group II.)

Recognizing the distinction between these two groups of arteriosclerotic gangrene, the fundamental principles involved in the treatment will be more readily understood. Cases falling into Group I are, in general, more amenable to conservative therapy and ultimate preservation of the limb because, as mentioned previously, there has been some attempt at the establishment of collateral circulation. Naturally, this is not quite as extensive or prolific as in the younger cases of thromboangiitis obliterans. The marked difference in formation of collateral circulation between the two conditions is well illustrated by arteriography.

DEVELOPMENT OF GANGRENE

It will be found that the most frequent point of origin of diabetic gangrene in Group I is a fissure in an interdigital space. This fissure is almost always caused by an infection of epidermophyton, which is so prevalent today. For this reason, the hygiene and prophylaxis of the diabetic foot must include serious consideration of ringworm infection of the interdigital spaces. Absolute cleanliness of the feet with the daily application of a mild antiseptic such as mercurochrome, metaphen, or weak iodine is imperative. The danger lies not so much in the ringworm itself as in the introduction of secondary, pyogenic invaders into the fissures and open lesions caused by the primary organisms. As soon as the secondary infection is established, the mischief is done. Local edema and infection soon cause small areas of superficial gangrene in the interdigital spaces. The pressure of the edema on the poorly nourished tissues causes further extension of the gangrene, usually toward the base of the adjacent toes. Thus the existing diminished blood supply to these digits is shut off completely and within a short time discoloration and gangrene are observed. This is usually excruciatingly painful, although in some rare instances, in hyposensitive individuals, discomfort may be slight. If the collateral circulation in the extremity is maintained, the gangrenous process may be confined to one or more toes—if not, further extension to the dorsum of the foot will ensue.

The proper management of diabetic gangrene in this early stage is of the greatest importance if the extremity is to be conserved. It must

be remembered, however, that only too often, even with the best of care, a diabetic arteriosclerotic limb must be sacrificed for an apparently insignificant lesion.

REST IN BED

At the first sign of impending gangrene, complete rest is imperative, not only because of the removal of local trauma but because of the necessity of maintenance of the limb in the horizontal position. If the extremity is held in the dependent position for even a short period of time, edema of the foot, and particularly of the involved area, soon appears. This causes greater pain and extension of the gangrenous process. Elevation of the foot is harmful since it causes further depletion of blood by the force of gravity. Hence, the horizontal position is preferable at all times. The natural physiologic advantages of complete rest are not to be neglected in the treatment of diabetic gangrene.

If conservative treatment eventually proves successful, the patient must remain in bed until complete healing has been achieved. This may prove impractical from the economic standpoint but is certainly imperative from the therapeutic standpoint.

SMOKING

The vasoconstricting action of smoking has been thoroughly demonstrated clinically and experimentally. For this reason it is advisable to prohibit completely the use of tobacco in all forms of peripheral arterial disease. Fortunately, this is not so great a problem in diabetic gangrene as it is in thromboangiitis obliterans. In the latter group, excessive cigarette smoking is the rule, while in the former, smoking, if indulged in at all, is usually extremely light.

LOCAL TREATMENT OF GANGRENE

The object of the local treatment of gangrene in the diabetic is to prevent, as far as possible, the development of secondary infection in the gangrenous area with its ultimate extension into the adjacent tissues. Gangrene, per se, is not as serious as the accompanying infection in diabetic subjects. Because of the menace of infection in diabetic gangrene, it is of the utmost importance that every precaution and care be taken in dressing and handling the involved parts. The crude practice of exposing a gangrenous foot under a cradle, with no dressing whatsoever, inviting contamination from flies, dirt, bedding and what not, is to be heartily condemned. In no other surgical condition is such treatment tolerated. Why, then, in a diabetic, whose susceptibility to infection is notorious?

In the incipient cases of interdigital gangrene and infection, daily gentle irrigation with warm boric acid solution is beneficial. This may be followed by the local application of a mild antiseptic, such as mercurochrome, and a protective covering of sterile gauze. If the infec-

tion has become frankly purulent, the irrigation should be followed by a small wet dressing of boric acid solution, which should be kept wet. As the purulent secretion decreases in amount and the tissues appear relatively clean, the wet dressing may be discontinued and a dry dressing or boric acid ointment may be applied.

The technic of the dressing is important. The parts should be handled only with either sterile gloves or with forceps. A real surgical respect for the gangrenous tissues is imperative in the treatment of diabetic gangrene.

Dusting powders are not recommended because of their tendency to cover up and conceal pus, thus often causing extension of the infection, even if trivial, into the deeper tissues.

Fig. 1.—Diabetic gangrene. Spontaneous amputation of toes. Gangrene of right big toe produced by burn of lamp and cradle.

If one is fortunate enough to secure a definite localization of the gangrenous process with the establishment of a line of demarcation, one should not be too impatient and attempt a quick removal of the dead tissue. I have seen a number of such attempts end in disaster. This is particularly true in the case of individual toes. In one instance, seen recently, excellent demarcation of a single toe had been established, but the attending physician attempted to hasten matters by forcibly twisting off the black toe with an artery clamp. The next day the patient complained of pain and swelling in the adjacent part of the foot and within forty-eight hours there was definite evidence of infection along the flexor tendon. In spite of radical incision and drainage, amputation of the leg had to be done. It is preferable to allow sufficient time for spontaneous separation of the dead parts.

A continuous wet dressing may be of help, or in some cases a daily foot bath of soap and water, with, of course, sterile precautions. In some instances careful dissection along the line of demarcation may be necessary. The choice of procedure will vary with each case and the judgment of the surgeon.

After the gangrenous tissues have been removed, it will usually be found that the proximal ulcer is partially epithelized. This can be encouraged to proceed either by a wet dressing of boric acid solution or by a bland ointment dressing such as boric acid.

Another common point of origin of gangrene is a small fissure on the heel. Prevention of this condition is usually simple if the possibility of its development in all cases of deficient circulation is kept in

Fig. 2.—Same case as shown in Fig. 1, healed except for residual ulcer of stump of left big toe.

mind. Daily inunction of the feet with either olive oil or lanolin should be a routine procedure by the patient, and its importance should be constantly stressed. Special attention to the heels is desirable.

Gangrene of the heel may also develop from constant pressure on the bedding while the patient is being treated for some other condition: I have found that a voluminous dressing of soft absorbent cotton over the heels is superior to the customary "doughnut" or cotton ring in avoiding this undesirable complication.

Once established, gangrene of the heel is difficult to control. However, with meticulous care, very satisfactory results can often be obtained. The avoidance of secondary infection is particularly impor-

tant in this condition. Again, cleanliness is essential. Gentle irrigation of the part, even when the gangrene is of minimal extent, should be a daily procedure.

Warm boric acid solution is excellent for the purpose, or a solution of azochloramide (1:3300) in saline may be preferred for its antiseptic action. Following the irrigation, the type of dressing will depend upon the nature of the local process. If there is no gross pus formation, boric acid ointment will be adequate. If there is considerable infection along with the gangrene, a wet dressing is preferable, using a solution of either boric acid or of azochloramide in saline. If the process becomes localized and under control, persistence in the daily dressing and a maximum of patience will usually yield gratifying results. While the heel lesions are as a rule extremely painful, much comfort can be obtained from a careful, comfortable dressing, properly applied.

Trauma is notorious as the cause of many cases of diabetic gangrene. Here again prevention is the important feature. Every known diabetic with deficient circulation should be warned, threatened, or even frightened in regard to the danger of home surgery such as cutting corns, calluses, or ingrown nails. Even the ordinary practice of trimming toenails should not be left in the hands of ignorant patients. The physician should not consider it beneath his dignity to properly perform this minor procedure for any patient with diabetes and arteriosclerosis.

Quite often it is not the patient who is to blame for an ill-advised ingrown toenail operation with its disastrous consequences. The physician is often at fault. Careful examination of the peripheral arterial circulation in a diabetic before undertaking any operative procedure on the extremity is absolutely imperative. The simple test for plantar ischemia[1] which I have described will readily disclose any deficiency in the arterial circulation of the lower extremities.

COLLATERAL CIRCULATION

Aside from the influence of infection, the progress and ultimate extent of the gangrenous process will depend primarily upon the adequacy of the collateral circulation that has either previously been established or is in the process of formation during treatment. Naturally, the extent of the existing collateral is of considerable consequence. For this reason, the intensive treatment of diabetic arteriosclerosis before the onset of gangrene should be carried out with much greater energy than is the present practice. Routine examination of the arterial circulation should be considered just as important as urine and blood sugar tests in the diabetic adult. The immediate institution of treatment directed to the stimulation of collateral circulation in such cases will, I feel sure, ultimately reduce the number

of cases of diabetic gangrene. The importance of prevention in this disease has not been sufficiently stressed.

In a case of established gangrene, efforts to aid in the development of additional collateral are necessarily handicapped, in contrast to the brilliant results obtainable in thromboangiitis obliterans. In the latter group, one deals with younger individuals with a remarkable tendency to the spontaneous development of collateral circulation. In the arteriosclerotic, the age is more advanced; spontaneous collateral is sparse and the reaction of stimulating agencies is weak. In addition, the older arteriosclerotic usually has an associated cardiac or renal impairment, or both, which adds more therapeutic difficulties. For these reasons, it is imperative that in the treatment of diabetic gangrene one is constrained to limit his enthusiasm to simple and safe procedures only, avoiding the spectacular, dangerous and impractical methods of treatment advocated only too often.

HEAT

In dealing with gangrene one must not lose sight of the fact that the local condition is usually only a small part of the entire extremity. Gangrene of one toe may be the result of a clot located in the external iliac artery. It must also be remembered that while one or more toes may be dying and cold, the remainder of the extremity is very much alive and capable of retaining and giving off a considerable amount of heat. Preservation of the natural heat of the entire extremity is a simple procedure. It can readily be attained by wrapping the limb in toto from groin to toes in a soft, warmth-retaining covering such as cotton or lamb's wool.

The use of external heat in diabetic gangrene, such as is obtained from an incandescent lamp or other source, is objectionable from two very important angles. In the first place, the danger of burns from accidental contact with the lamp or other source of heat is notorious. Because of the frequent occurrence of these disastrous burns, the use of the cradle and lamp is condemned. The second objection to external heat is the inability of the superficial tissues of the heated extremity to respond properly to the raised temperature applied. Increased heat requires a greater blood flow and an increased local metabolism of the superficial tissues. Neither of these is possible in these blood-starved extremities, resulting in considerable danger in the form of burns or of spreading gangrene, not to speak of the excellent incubation provided for saprophytic organisms lying dormant in the gangrenous tissues.

INTRAVENOUS INJECTIONS OF HYPERTONIC SALINE

The immediate increase in peripheral pulse amplitude following the intravenous injection of hypertonic saline solution is easily demonstrated with the oscillometer. Instead of the 5 per cent solution ad-

vocated in thromboangiitis obliterans, I have used weaker solutions (2 per cent and 3 per cent) in the treatment of diabetic gangrene and believe that they have definitely contributed to the successful outcome of many cases.[2] An additional advantage in the use of hypertonic saline solution in diabetic gangrene is its tendency to lessen the blood sugar, as observed by Glass and Beiless (1930)[3] and Thompson and McQuarrie (1934).[4]

If there are no contraindications, such as a poor myocardium, severe nephritis, or hypertension, saline injections may be given three times a week. In younger patients 300 c.c. of 3 per cent sodium chloride solution suffices, while in older individuals (over 60) 200 c.c. of 2 per cent saline solution will, in most cases, produce an increase in peripheral pulse amplitude, with consequent stimulation of collateral circulation.

MECHANICAL APPARATUS

The use of mechanical aids to improve collateral circulation in arteriosclerotic extremities is attended with considerable danger, particularly in the presence of infection. For this reason the employment of suction and pressure, venous compression, and other forms of mechanical therapy is not recommended in diabetic gangrene. The results reported by others, as well as my own observations, do not as yet warrant the routine use of these mechanical aids in this form of arterial disease. If the suction pressure boot could be so constructed as to affect the entire extremity as high as the pelvis, instead of the lower portion only, some theoretical benefit might be obtained. In their present form, it is questionable whether more than compression and distention of the superficial veins is obtained with the various suction pressure apparatuses now available. The harmful effect of the exercise of intermittent venous compression alone is obvious in infected diabetic gangrene.

SYMPATHECTOMY AND GANGLIONECTOMY

The organic basis of the rigid arterial walls characteristic of arteriosclerotic gangrene and the known sparse collateral circulation in this condition preclude the possibility of any benefit from operative interruption of the sympathetic pathways in this malady. I believe this opinion is now generally shared by experienced workers in peripheral arterial diseases.

INDICATIONS FOR AMPUTATION

The two chief indications for amputation in diabetic gangrene are (1) uncontrollable spread of gangrene of such extent as to destroy the weight-bearing part of the foot and (2) spreading infection that cannot be controlled by incision and drainage or other surgical measures.

As mentioned previously, diabetic gangrene may limit itself to one or more toes, or to a restricted area of the heel or dorsum of the foot. In such cases, spontaneous separation of the gangrenous parts can occur with subsequent healing of the resultant ulcer. Unfortunately, however, this does not occur with as great frequency as in thromboangiitis obliterans, where this is the rule rather than the exception. When, in diabetic gangrene, the gangrenous process continues to spread to important parts of the foot or involves the entire foot, en masse, amputation must be performed. In this progressive type of case, the pain is practically uncontrollable because of the comparatively large areas of tissue involved in the mortifying process. Peripheral nerve section will not influence this type of pain. Furthermore, operative incisions in the leg are not entirely without danger in diabetic gangrene. Where the gangrene is limited to one or more toes, the pain is negligible and usually subsides completely as soon as the line of demarcation is established.

Infection.—This is by far the commonest indication for amputation in diabetic gangrene.

The situation here is again quite different from that in thromboangiitis obliterans. In the latter, gross infection of the gangrenous parts is entirely harmless and rarely extends into the adjacent healthy tissues. In the diabetic arteriosclerotic, however, a limb with a minimum amount of gangrene must often be sacrificed because of uncontrollable infection.

Even in cases with so-called dry gangrene of a single toe it is important to take all precautions in the prevention of infection. Daily irrigation of such parts with warm boric acid solution, as described previously, followed by the application of a mild antiseptic such as picric acid or mercurochrome particularly along the line of demarcation, is necessary. A sterile dry gauze dressing is imperative. Sometimes, in spite of all precautions, a dry gangrene of the toe changes with alarming rapidity into a rapidly spreading infection of the foot and leg. A very common route of infection is into the plantar tissues and along the tendons or fascial spaces. There may be no immediate rise of temperature to herald the approach of this infection; pain may not be increased. The only evidence of such extension may be exquisite tenderness at the base of the gangrenous toe, along the line of the tendon. In the more advanced cases, gentle pressure at this point will cause the extrusion of a drop of thick pus from the proximal part of the line of demarcation. Careful judgment is essential at this time if the limb is to be conserved. If convinced of the presence of pus in the plantar tissues, immediate incision and drainage are in order. This must be done under general anesthesia and the incision should be planned very carefully to avoid opening uninfected tendons or

fascial spaces. Incision, as a rule, should be made in a longitudinal direction, starting at the base of the toe. The involved area should be packed wide open and wet dressings applied.

If the collateral circulation is adequate, such incision and drainage may be successful; if not, gangrene of the incised tissues will usually follow.

Unfortunately, in most of these cases, the plantar infection burrows deeper and may even ascend along the tendons into the leg. At this time the diabetes usually runs wild. The blood sugar rises and the urinary sugar increases in spite of heroic increases in insulin dosage. In most of the cases, insulin appears to have no effect. I believe that in diabetic gangrene a progressively higher insulin requirement is a better indication of spreading infection than a rise in temperature.

If the infection subsides and remains localized with incision and drainage or wet dressings alone, conservative measures aimed at demarcation and removal of the gangrenous parts may be continued. If, however, the infection cannot be checked, even in the presence of minimal gangrene, immediate amputation of the limb is justified.

TECHNIC OF AMPUTATION

It seems logical to assume that any case of diabetic gangrene severe enough to require ablation of the extremity should be subjected to that type of operation which has been proved to be safest and simplest. I have had the most gratifying results with simple circular no-flap amputation through the lower third of the thigh. The experience of McKittrick and Root,[5] Eliason and Wright,[6] Kuhns and Wilson[7] bears out this opinion. Plastic operations of various types are objectionable here because of the damaged circulation of the extremity and the presence of diabetes. I favor general anesthesia, particularly cyclopropane, because of the stimulating effect of the greater percentage of oxygen that can be given with this gas.

Thorough preoperative cleansing of the skin at the site of incision is carried out by brisk application of benzine followed by alcohol. Iodine is next applied in the usual manner. No tourniquet is used. A circular incision with an ordinary scalpel is made about two inches above the upper border of the patella. This scalpel is now discarded and a fresh one is used for the deeper tissues. Fascia, muscles, and other soft parts are severed in one plane with precise strokes, avoiding unnecessary trauma as by violent sponging or hacking strokes. All bleeding vessels are clamped at once. At this low level of amputation, the popliteal rather than the femoral artery is encountered in the deep medial portion of the thigh, rather close to the femur. If the pulsation of the artery can be felt, it and the accompanying vein are doubly caught and severed between the clamps. Quite often the pulsation cannot be felt because of calcification or thrombosis or both.

In such a case a hard cord can be palpated, which should be clamped and cut along with the accompanying vein. Having severed all soft parts down to the bone, it is imperative that all bleeding points be

Fig. 3.—Healed diabetic gangrene involving four toes. Gangrene precipitated by exposing foot under a lamp and cradle.

Fig. 4.—Diabetic gangrene. Amputation stump eight days after operation. Primary union.

properly secured before sawing, to avoid later unnecessary trauma incident to hunting for hidden bleeders. A warm saline towel is now spread over the proximal tissues and these are retracted back along the femur by gentle pressure until about two inches of bone is ex-

posed. The periosteum of the femur is now cut with a sharp scalpel and scraped distally. The femur is sawed through at this level (about two inches above the line of incision). Frequent changes of towels are essential to maintain a clean operative field at all times.

After proper division of the femur, the soft parts, after removal of all artery clamps and tying of the vessels, should come together with no tension whatsoever over the end of the bone. The muscles are approximated (anteroposterior) with plain catgut sutures. The fascia is closed with plain catgut and the skin edges approximated very carefully with silkworm-gut. No drainage is necessary.

A light dressing is applied to the stump and held in place by adhesive tape. There is no advantage in the use of bulky dressings or clumsy protective devices, such as wood slats or other trimmings. Postoperative elevation of the stump on a pillow is advisable for a few days.

As a rule the temperature falls below 100° F. on the third day. If so, the patient may be out of bed from that time on, a distinct advantage in elderly patients, particularly diabetics. If the stump remains clean, sutures may be removed on the sixth or seventh day and the patient may be discharged from the hospital on the eighth day. Ten days is about the average duration of hospital stay, if primary union has been attained.

If there is evidence of infection in the stump, which is usually superficial, only one or two skin sutures need be removed and a wet dressing applied for a few days. Subsequent healing is usually uneventful.

The advantages of this type of operation over the older methods of leaving stumps wide open or inserting drains are so obvious as to require no comment.

Statistical studies of a series of these cases will be published in a subsequent communication.

CONTROL OF DIABETES

During the period of conservative treatment of diabetic gangrene it is necessary to keep the patient reasonably sugar free by the usual methods. The administration of insulin according to frequent examinations of urine during the day is the preferable plan where practicable. It is not necessary to try to maintain the blood sugar and urine absolutely normal throughout the day and night in these patients, who are mostly elderly, but gross carelessness on the part of attendants (if the patient is treated at home) should not be permitted. As mentioned previously, the onset of infection in the foot will call for increasingly larger doses of insulin.

The pre- and postoperative intravenous administration of large amounts of fluid and glucose with sufficient insulin coverage is neces-

sary only in dehydrated patients or in those whose general preoperative care has been neglected for a long time. The average, well-treated diabetic needs no special preparation either before or after the operation.

SUMMARY

Arteriosclerosis obliterans plus diabetes is a serious condition requiring intensive treatment as soon as the diagnosis is made.

Prevention of diabetic gangrene is possible if the diagnosis of deficient circulation is made in its incipient stages and proper treatment instituted at once.

Conservative treatment of diabetic gangrene is often successful providing meticulous care is given to the local condition, with due regard for asepsis and antisepsis. Particular attention should be given ringworm infection of the interdigital spaces in diabetes.

Uncontrollable infection or massive, nondemarcating gangrene justifies amputation in diabetic gangrene.

Simple, circular amputation through the lower third of the thigh, with tight closure of the stump and no drainage, is the operation of choice.

REFERENCES

1. Samuels, S. S.: The Early Diagnosis of Thromboangiitis Obliterans: A New Diagnostic Sign, J. A. M. A. **92**: 1571, 1929.
2. Samuels, S. S.: The Diagnosis and Treatment of Diseases of the Peripheral Arteries, New York and London, 1936, Oxford University Press.
3. Glass, J., and Beiless, I.: Chlorhaushalt und Kohlenhydratstoffwechsel. Einfluss hypertonischer Kochsalzlösung auf den Blutzucker bei Diabetes, Ztschr. f. d. ges. exper. Med. **73**: 801, 1930.
4. Thompson, W. H., and McQuarrie, I.: Effects of Various Salts on Carbohydrate Metabolism and Blood Pressure in Diabetic Children, Proc. Soc. Exper. Biol. & Med. **31**: 907, 1934.
5. McKittrick, L. S., and Root, H. F.: Diabetic Surgery, Philadelphia, 1928, Lea & Febiger.
6. Eliason, E. L., and Wright, V. W.: Diabetic and Arteriosclerotic Gangrene of the Lower Extremities, Surg., Gynec. & Obst. **42**: 753, 1926.
7. Kuhns, J., and Wilson, P. D.: Major Amputations: Analysis and Study of End-Results in Four Hundred and Twenty Cases, Arch. Surg. **16**: 887, 1928.

STRUMA LYMPHOMATOSA (HASHIMOTO)

A Survey of the Literature and Report of a Case

C. Marshall Lee, Jr., M.D., and E. J. McGrath, M.D.,
Cincinnati, Ohio

(From the Department of Surgery of the College of Medicine of the University of Cincinnati and the Cincinnati General Hospital)

VARIOUS forms of chronic thyroiditis have long been known to surgeons and pathologists, and certain types, in which a specific etiologic background can be demonstrated, although sufficiently rare to arouse interest when observed, have ceased to excite more than passing comment. Among these, tuberculous, syphilitic, and parasitic thyroiditis may be mentioned. In certain other types the cause remains undetermined, and although these have been recognized for over forty years as being distinct from the above group, they are still the subject of lively controversy and their status in the nosology of thyroid disease remains to be established.

As far back as 1868, Semple[1] reported a case of "fibroid enlargement of the thyroid body" in a woman fifty years of age. The pathologic description of the autopsy specimen closely resembles that of what is today termed Riedel's struma, but the picture is complicated by the fact that the patient ultimately died of pulmonary tuberculosis.

In 1885, Bowlby[2] described the case of a woman aged forty-two years who died, after a belated operation, of obstructive symptoms from an extensive fibrosis of the thyroid which, in the three years of its known existence, had involved the surrounding structures of the neck and even of the mediastinum but which showed no evidence of remote metastases. In spite of the fact that the tissue looked perfectly benign microscopically and consisted only of dense fibrous tissue, Bowlby felt that its extensive involvement of the surrounding structures was evidence of malignancy, and he tentatively reported it as an infiltrating fibroma or sarcoma of the thyroid.

Eleven years later Riedel[3] described a case of chronic thyroiditis in a man aged forty-two years, which he had preoperatively mistaken for a carcinoma, and in which he had been agreeably surprised to see his patient recover after resection of a small fragment. Microscopically, the picture was one of chronic inflammation with extensive fibrosis and he called the condition Eisenharte strumitis or iron-hard strumitis, and subsequently reported a number of similar cases. One of these, in a child four years of age, is the youngest case on record. His first report included two cases and he summarized the findings as follows:

Received for publication, March 13, 1937.

"In both cases we found a chronic inflammation. If one looks at the microscopic sections, one sees an infiltration of round cells in normal thyroid tissue which is more or less destroyed by these round cells. The microscopic picture gives no indication of how hard the tumor is. One would expect to find fibrous tissue. However, the predominant finding is round cells. The tissue appears much harder before operation. This must be explained by the numerous dense adhesions to the surrounding structures, especially to the blood vessels, nerves, and trachea. All these adhesions are as dense as leather. They are extremely vascular. One does not make any progress in attempting to loosen the tumor. The great vessels appear to be encased in scar tissue. One can cut them through above and below the tumor, but it is impossible to separate them from the tumor mass. The recurrent laryngeal nerves are embedded in scar tissue and can scarcely be identified. The trachea is so softened that one can imagine it to be already perforated. Even the most malignant tumor is easier to separate than this tissue which is caused by chronic inflammation."

Since Riedel's description of the condition, many cases of this type of thyroiditis have been reported under a wide variety of names, such as primary cancériform inflammation of the thyroid (Tailhefer), primary chronic inflammation of the thyroid (Berry), la thyroidite ligneuse (Delore and Alamartine), benign granuloma of the thyroid (Ewing), lymphadenoid goiter (Williamson and Pearse), and later on simply Riedel's struma.

In 1912, Hashimoto[4] described four cases in which the subjective symptoms were similar to those reported by Riedel, but in which the thyroid tissue was virtually replaced by lymphoid tissue. He called this condition struma lymphomatosa and described differences between this and Riedel's struma. He said in part:

"If we summarize the present clinical observations, we had four patients, all female, all beyond forty years of age, not living in a goitre district and with a family history negative for goitre. . . . They had never been seriously ill, and were without any of the serious infectious diseases frequently followed by disease of the thyroid, especially strumitis. Lues and tuberculosis were excluded clinically. The thyroid enlargement was discovered incidentally in all cases.

"We found a not very rapid enlargement of the thyroid, with good general health. . . . Both lobes were involved in all cases. . . . Severe symptoms of pressure such as dyspnoea and aphonia have never been present. Only in one case, a slight hoarseness appeared before operation combined with incomplete closure of the vocal cords, which can be explained by unsatisfactory function of the arytenoid muscle. Not a trace of inflammation of the thyroid could be found. The mass was freely movable but the consistency was usually so firm that one would think of malignancy or Riedel's strumitis. There was neither regional nor generalized lymphadenopathy. No other visceral abnormality was found.

"The operative findings did not demonstrate much adherence to adjacent structures, as in cases of Riedel's goitre, which is accentuated by this author (Riedel?). Postoperative hoarseness was present in all cases, although slight in amount. In the postoperative course, an edema of the entire body is said to have occurred, disappearing after the internal administration of thyroid. Special attention must be called to the fact that all these cases required a long convalescence before complete recovery, although the usual cases of benign goitre had a postoperative course without complications.

"The chief (histologic) findings in all cases were:

"1. Formation of numerous lymphatic follicles.

"2. Striking changes in the epithelial tissue of the acini (atrophy) of the thyroid and their contents (absence of colloid).

"3. Extensive proliferation of connective tissue, and diffuse round cell infiltration (lymphocytes and plasma cells)."

Williamson and Pearse,[5] in 1929, expressed the opinion that the condition represents a pathologic variant of a normal function of the thyroid, namely, the elaboration of what they term a lymphogenic secretion. On the basis of McCarrison's[6, 7] work on vitamin A deficiency in albino rats and his experimental production of a picture closely simulating human lymphadenoid goiter by means of an iodine-containing but vitamin-deficient diet, they postulated that this might play a part in the human disease but offered no supporting evidence. They contended that there is a close relationship between Riedel's struma and Hashimoto's struma.

That this is an untenable view is pointed out by Joll[8] and Graham and McCullagh[9] for the following reasons:

1. Hashimoto's struma is confined almost entirely to women over the age of forty-five years, while Riedel's disease usually occurs in adults, but may appear at any age, and men are nearly as often affected as women.

2. Regardless of operative treatment, patients with lymphadenoid goiter tend to develop myxedema, frequently preoperatively. Riedel's disease, even after extensive resection, rarely leads to defective function.

3. Lymphadenoid goiter is a diffuse condition from the outset, and no part of the gland escapes. Localization to a lobe or part of a lobe is common in Riedel's struma.

4. Widespread formation of delicate connective tissue is characteristic of the late stages of lymphadenoid goiter, while dense fibrosis, comparable to scar tissue or keloid formation, is found even in the earlier stages of Riedel's disease.

In regard to incidence, only one case which might be taken for Hashimoto's struma has ever been reported in a man. However, although this case is frequently quoted in the literature as one of Hashimoto's struma, it was reported by Louise H. Meeker herself, with the corroboration of Ewing, as one of Riedel's struma, and judging from her description and the ten plates included with the article, her diagnosis seems fully justified; and this leaves the reported cases of lymphadenoid goiter confined exclusively to women. In a very comprehensive study published in December, 1935, J. G. Lee[11] was able to collect from the literature only twenty-six cases of Hashimoto's struma, including his own three cases, and ninety cases of Riedel's struma including nine of his own.

In analyzing these cases he did not find a marked difference in age incidence, the average for Riedel's disease being 42.8 years and for Hashimoto's struma, 47.6 years. His youngest case of the latter was a woman aged twenty-six. In Riedel's struma the sex distribution was 32 per cent males and 68 per cent females, while in Hashimoto's struma the proportion was 96 per cent females to 4 per cent males, the latter representing the single case reported by Meeker (vide supra).

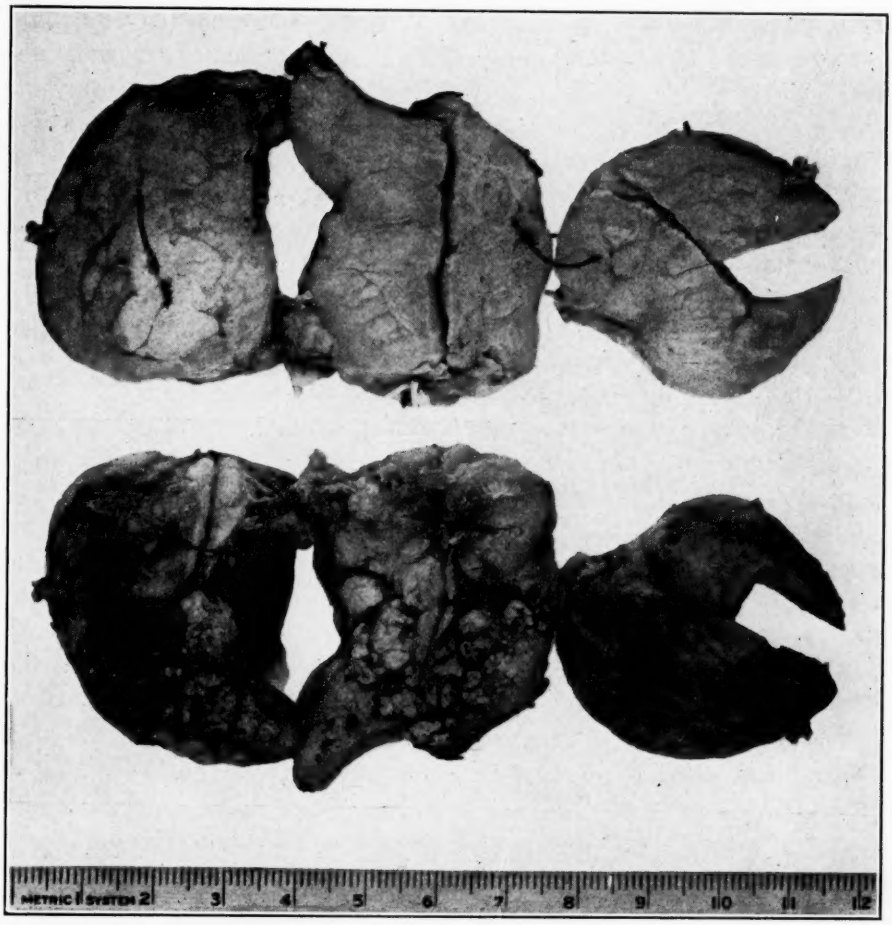

Fig. 1.—Photograph of the gross specimen after formalin fixation.

Various other observers, in analyzing collected cases, report a slightly higher age incidence in Hashimoto's struma, namely, 52.4 years (Graham[12]), 53.0 years (Gilchrist[13]), and 55.5 years (Clute, Eckerson, and Warren[14]), while in Riedel's struma the general average is 40.9 years.

The duration of symptoms at the time of first observation is, if anything, slightly longer in Hashimoto's struma than in Riedel's disease. The average duration in the former is twenty-five months and in the

latter is eighteen months (average from Gilchrist's and J. G. Lee's reports), which militates against the view that Riedel's disease is a late stage of lymphadenoid goiter.

Although no specific figures are available, the occurrence of preoperative myxedema is not reported in any of the cases of Riedel's disease that have been encountered in the literature, while this is a common event in Hashimoto's struma. Postoperative myxedema has occurred in 40 per cent of the cases of lymphadenoid goiter, and in 20 to 25 per cent of cases of Riedel's disease. The tendency of struma lymphomatosa to develop myxedema is strongly emphasized by Hertzler,[15] and eight of the nine cases reported by Clute, Eckerson, and Warren[14] developed myxedema, while the ninth was lost sight of and her later course could not be followed.

In every case of Hashimoto's struma the entire gland has been involved, while in Riedel's struma 30 per cent of J. G. Lee's series, and 49 per cent of Gilchrist's series showed only unilateral involvement. Furthermore, no case of Hashimoto's struma has been reported in which there was involvement of the perithyroid tissues, while 78 per cent of Gilchrist's series and 80 per cent of J. G. Lee's series of Riedel's disease showed cervical adhesions at operation.

The etiology of both conditions remains obscure. The records of the majority of the reported cases are incomplete, but where it is included, a history of some previous infectious disease or the finding of focal infection is quite common in Riedel's struma. Clute and Lahey[16] in 1932 included Riedel's struma in their group of chronic thyroiditis either primary in the gland or secondary to general infection but did not mention Hashimoto's struma. In a later paper, Clute, Eckerson, and Warren noted a possible infectious factor in several of their nine cases of Hashimoto's struma.

The suggestion of dietary deficiency offered by Williamson and Pearse[5] has already been mentioned; and Graham and McCullagh,[9] in addition to infectious diseases and focal infections, consider the factor of antecedent hyperthyroidism as a possible predisposing cause. They point out that although evidence of this cannot always be demonstrated, it is recognized that well-advanced myxedema is not infrequently seen in which there is no history of previous toxicity and yet the pathologic picture is that of a burned-out, toxic goiter. They consider it premature, therefore, to rule out hyperthyroidism as a precursor of struma lymphomatosa, with a possible direct relationship.

It becomes evident, therefore, that a careful analysis of a large series of cases in which complete data are available will be necessary if the status of these two diseases of the thyroid is to be established. A survey of the available literature through the end of 1936 adds fifteen cases of Hashimoto's struma to the twenty-six collected by J. G. Lee, making a total of forty-one cases. In most of these, however, insufficient detail is presented to allow a comprehensive analysis.

Fig. 2.—Photomicrographs from various portions of the gland, showing generalized lymphocytic infiltration and well-developed germinal centers. (×200)

The condition is so unusual that the accumulation of a considerable series in any one clinic is a prolonged process and it is to be hoped that sufficient cases will be reported in the next few years to make such an analysis possible. With this in mind, the present case is recorded in some detail.

CASE REPORT.—The patient, Mrs. A. F., was a white woman aged fifty years and a gravida ii, para ii, four years past the climacteric. She was admitted to the

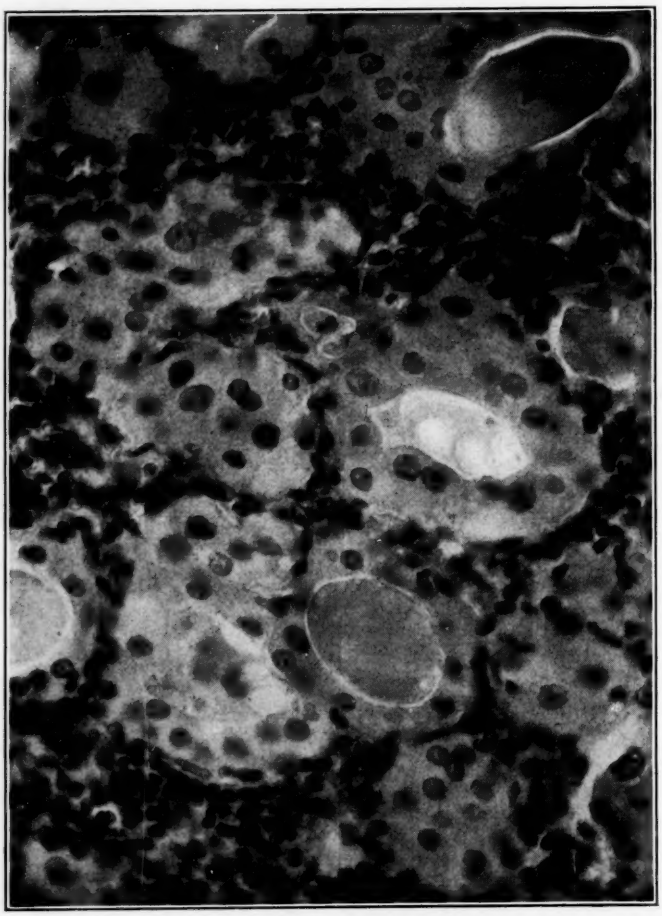

Fig. 3.—Photomicrograph showing the character of the acinar epithelium. (×800)

hospital October 29, 1936, with a chief complaint of "nervousness." She dated the onset of her present illness from an attack of "influenza" two years previously. She knew at that time that she had a goiter but was not sure how long she had had it, and as far as she knew, it had never given her any symptoms. After recovery from the influenza she began having attacks of nervousness, which seemed to be intermittent, and during which she was extremely irritable and felt, herself, that she had appreciable personality changes. This condition continued without notable change and without increase in the size of the goiter for about a year. In February, 1936 (six months before admission), she had another attack of influenza, after which all of her symptoms were exaggerated. During an attack of nervousness and ir-

ritability, there was a dull occipital headache, and she began to notice an occasional swelling of the hands and of the infraorbital region, and this was accompanied by mild tingling and numbness of the hands. At the same time her skin began to become noticeably dry. There was mild anorexia and constipation, but no loss of weight, and the patient noticed that she felt cold all the time. She had never noted excessive perspiration at any time, and the only symptom referable to her heart was a mild palpitation on moderate exertion. Obstructive symptoms were absent. For about a year previous to admission the patient had been under the care of her family physician, who had been treating her with Lugol's solution, but no B.M.R. determination had been made. She was able to carry on her work until a week before admission but then retired to bed and was sent to the hospital by her physician.

Past History: The patient had the usual childhood diseases, but except for an attack of multiple furunculosis eight years previously and several mild attacks of right upper quadrant pain, nausea, vomiting, and slight transient jaundice, her general health had been good.

Family History: This was essentially negative except that her father had died of "dropsy" at the age of sixty.

On admission T.P. and R. were 98.6, 98, and 18. B.P. 154/90. Patient was well developed and nourished and did not appear acutely ill. Her skin was dry and thick, especially over the hands, and there was an appreciable thickening and enlargement of the tongue. The thyroid was moderately enlarged, the right lobe slightly larger than the left, and quite firm, but not appreciably nodular. Hgb. 76%; R.B.C. 4.78; W.B.C. 8,700; Schilling count—Myelo. 2%; PMN 78%; Lymph. 18%; LMN 1%; Eos. 3%. Urine negative, Wassermann not reported. B.M.R. -13%.

Under a diagnosis of toxic diffuse goiter with involution, a subtotal thyroidectomy was done, and at operation the gland, which was removed without difficulty, was found to be smooth, pale, and rather firm.

Postoperative course was uneventful except that on the third day she had a mild attack of right upper quadrant pain, with some tenderness, and mild nausea and vomiting. Two attempts at gallbladder visualization showed total absence of shadow. The attack subsided promptly, and the patient was discharged on daily doses of thyroid extract.

The pathologic report was as follows: "This specimen consists of two rounded masses of tissue identified as thyroid gland. They are joined by a slender capsular strand, and only a small portion of the isthmus is included. The right lobe measures 5½ by 3½ by 2 cm., and the left, 5 by 3½ by 3 cm. There are no grossly apparent nodulations and both masses are well encapsulated. The cut surface presents a rather pale, pinkish appearance and is homogeneous throughout. There is no grossly visible colloid and the cut surface is smooth and unbroken by visible fibrous septa. On microscopic examination sections from various portions of both lobes show an identical picture. The most striking feature is an extensive infiltration of the entire tissue by lymphocytes, and numerous secondary nodules, complete with germinal centers, are present. The acini are uniformly small and contain little or no colloid. Such colloid as is present stains poorly and much of it is basophilic. The lining epithelium of the acini shows cells which are pale and swollen, and in many the cells fill the entire lumen. Thus the lining epithelium appears very inactive and the pattern certainly does not suggest formation of any new acini. The capsule of the gland is dense and somewhat thickened, but the massive infiltration of lymphocytes is confined within the parenchyma of the gland, and there is no evidence of extension of the process through the capsule. The connective tissue in the gland appears swollen and degenerated, and much of it is becoming hyalinized."

Diagnosis: Struma lymphomatosa (Hashimoto).

COMMENT

An interesting feature of the case is that it presents two of the three aspects mentioned above in connection with possible etiologic relationships. Not only is there a history of two attacks of influenza and one of multiple furunculosis, but there was strong evidence of a focus of infection in the gallbladder. Moreover, her history and clinical course indicate a definitely toxic thyroid on which unmistakable signs of myxedema were superimposed.

Although Ewing states that struma lymphomatosa is an early stage of Riedel's disease, Graham's objections to this view are unquestionably impressive. While the former disease may occur in considerably younger persons than Graham's survey indicated, the tendency is certainly toward a higher incidence in older women, and this and the longer average duration of symptoms must bear some weight in a consideration of the disputed relationship between the two diseases. Moreover, in Hashimoto's struma the diffuse character of the lesion, its limitation to the gland parenchyma without extrathyroidal adhesions, its common association with myxedema, and its apparent limitation to female patients are in quite striking contrast to the usual course of Riedel's disease. These features together with the rather distinctive microscopic findings in the two conditions leave one with the impression that they must be regarded as separate entities.

REFERENCES

1. Semple: Fibroid Enlargement of the Thyroid Body With Enlarged Cervical Nodes, Tr. Path. Soc. Lond. **20**: 397, 1868-69.
2. Bowlby, A. A.: Infiltrating Fibroma (? Sarcoma) of the Thyroid Gland, Tr. Path. Soc. Lond. **26**: 420, 1884-85.
3. Riedel: Die chronische, zur Bildung eisenharter Tumoren fuhrende Entzundung der Schilddruse, Verhandl. d. deutsch. Gesellsch. f. Chir. **25**: 101, 1896.
4. Hashimoto, H.: Zur Kenntnis der lymphomatosen Veranderung der Schilddruse (Struma Lymphomatosa), Arch. f. klin. Chir. **97**: 101, 1912.
5. Williamson, G. S., and Pearse, I. H.: Lymphadenoid Goiter and Its Clinical Significance, Brit. M. J. **1**: 4, 1929.
6. McCarrison, Robert: Note on the Experimental Production of Lymphadenoid Goiter in Rats, Brit. M. J. **1**: 5, 1929.
7. McCarrison, Robert: Studies in Deficiency Diseases, London, 1921, Oxford University Press.
8. Joll, Cecil A.: Diseases of the Thyroid Gland, St. Louis, 1932, The C. V. Mosby Company.
9. Graham, A., and McCullagh, E. P.: Atrophy and Fibrosis Associated With Lymphoid Tissue in the Thyroid, Arch. Surg. **22**: 548, 1931.
10. Meeker, Louise H.: Riedel's Struma Associated With Remnants From the Post-Branchial Body, Am. J. Path. **1**: 57, 1925.
11. Lee, J. G.: Chronic Nonspecific Thyroiditis, Arch. Surg. **31**: 982, 1935.
12. Graham, A.: Riedel's Struma in Contrast to Struma Lymphomatosa, West. J. Surg. **39**: 681, 1931.
13. Gilchrist, R. K.: Chronic Thyroiditis, Arch. Surg. **31**: 429, 1935.
14. Clute, H. M., Eckerson, E. B., and Warren, S.: Clinical Aspects of Struma Lymphomatosa (Hashimoto), Arch. Surg. **31**: 419, 1935.
15. Hertzler, A. E.: Surgical Pathology of the Thyroid Gland, Philadelphia, 1936, J. B. Lippincott Company.
16. Clute, H. M., and Lahey, F.: Thyroiditis, Ann. Surg. **95**: 493, 1932.

THE SHOCK SYNDROME IN LIVER PERITONITIS

An Interpretation of the Rôle Dog Liver Bacteria Play in Causing Rapid Death

H. E. Martin, M.D., and H. M. Trusler, M.D., Indianapolis, Ind.
(From the Department of Surgery and the Research Division of Indiana University School of Medicine, Landon Research Fellowship, Eli Lilly Research Fellowship)

THE possible formation of toxic substances by autolysis of body tissues is an old problem which has been intensively studied. Renewed interest was aroused by the investigations of Mason, Davidson, Matthew and Rastello,[1] who reported that autolysis of dog liver in vivo was highly toxic and caused rapid death. The numerous investigations which were stimulated by this observation have resulted in the advancement of different theories to explain the rapid death which follows intraperitoneal implantation of liver and bile salt preparations. Ellis and Dragstedt[2] reported experiments to show that the rapid death of the animal was intimately associated with an anaerobic bacterial peritonitis caused by bacteria which normally inhabit the adult dog liver. Andrews, Rewbridge, and Hrdina[3] concluded from their experiments that the adult dog liver as well as other tissues harbored the Welch bacillus and attributed rapid death to a Welch bacillus toxemia. Dvorak,[4] likewise, concluded that death was caused by exotoxins produced by dog liver bacteria which grew in the autolyzing liver fragments. We have been interested in this problem for a number of years and in our early studies[5, 6] we presented experiments to show that the bacteria recovered from the tissues of the dog produced no exotoxins. Furthermore, we demonstrated that the dog liver anaerobe differed from the Welch bacillus both in morphology and cultural characteristics. In a recent publication,[7] we showed that dogs subjected to intraperitoneal implantation of fresh, ground, adult dog liver die rapidly with all the laboratory and clinical signs of severe shock. Death was associated with an anaerobic bacterial peritonitis. We found, however, that if fresh liver was ground with an equal quantity of salt solution and strained so that the gross connective tissue elements were removed, the resulting suspension of liver cells was much less toxic than the whole liver. When these cellular elements of fresh dog liver were placed intraperitoneally, the animal survived even though considerable amounts of the liver substance remained unabsorbed for several days. On the contrary, when equivalent amounts of blood vessel, bile duct, and connective tissue elements of liver, or

Received for publication, March 22, 1937.

the whole liver substance were placed intraperitoneally the animal rapidly died with severe shock associated with anaerobic bacterial peritonitis.

We have extended our experiments upon fresh dog liver and have also investigated the effects of placing intraperitoneally various preparations of fresh liver sterilized by autoclaving as well as different preparations of incubated liver. In the following experiments we will present observations which may explain many of the conflicting reports of different investigators. We also submit what, in our opinion, may be the correct interpretation of the rôle played by dog liver bacteria in causing rapid death. Since we used different groups of liver preparations in our studies we shall present our experiments under these leads.

FURTHER EXPERIMENTS UPON FRESH, GROUND, ADULT DOG LIVER

All investigators of this problem agree that when 30 or more grams of fresh, adult dog liver are placed intraperitoneally the animal dies, usually within 24 hours. When this quantity is used, the amount per kilogram of the animal's weight has little influence upon the time of survival. In a previous paper,[7] we reported that the cellular elements of liver were less toxic to the experimental animal than equivalent amounts of whole liver, or the blood vessel, bile duct, and connective tissue fraction. The amount of cellular elements used in these earlier experiments was approximately 70 gm. In the following experiment an attempt was made to ascertain the minimal amount of cellular element of fresh liver which would cause rapid death when placed intraperitoneally.

Experiment 1.—The cellular elements were prepared as described previously[7] and varying amounts placed intraperitoneally in 6 dogs through a small laparotomy incision. Two dogs each received approximately 140 gm. of cellular elements together with equal volumes of normal saline. The remaining four animals each received approximately 100 gm. of cellular elements together with 100 c.c. of normal saline. Blood counts, hemoglobin determinations, and total nonprotein nitrogen estimations were done on samples of blood removed before the liver substance was administered and repeated 18 hours later. Samples of peritoneal exudate were removed from each of the animals 18 hours after the introduction of liver for bacteriologic smear and culture. Table I shows the results of the experiment.

The experiment demonstrates that the nontoxicity of the cellular elements of liver is relative, and apparently depends upon bacterial growth in the peritoneal cavity. When more than 100 gm. of cellular elements were introduced, the dogs developed bacterial peritonitis and died within 30 hours with shock findings similar to those seen when animals are given lethal amounts of fresh, whole liver. When less than 100

TABLE I

THE EFFECT OF PLACING VARYING AMOUNTS OF THE CELLULAR ELEMENTS OF FRESH, ADULT DOG LIVER INTRAPERITONEALLY

DOG	AMOUNT OF CELLULAR ELEMENTS PLACED INTRAPERITONEALLY		RESULT	BLOOD ANALYSES						PERITONEAL EXUDATE REMOVED 18 HOURS AFTER INTRODUCTION OF LIVER	
				NORMAL			18 HOURS AFTER INTRODUCTION OF LIVER				
	TOTAL GM.	GM. PER KILO. OF ANIMAL'S WEIGHT		R.B.C. MILLION PER C.MM.	HB.	T.N.P.N.	R.B.C. MILLION PER C.MM.	HB.	T.N.P.N.	SMEAR	CULTURE
54	140	14.0	Died in 22 hr.	6.55	13.0	25.0	9.45	18.0	38.0	Positive for dog anaerobe	Positive for dog anaerobe
55	140	13.5	Died in 19 hr.	5.70	13.5	21.6	8.20	19.0	70.0	Positive for dog anaerobe	Positive for dog anaerobe
56	100	7.5	Died in 30 hr.	7.20	13.0	29.0	7.44	17.0	48.0	Positive for dog anaerobe	Positive for dog anaerobe
57	100	6.3	Survived	8.40	14.0	34.0	9.55	16.5	37.0	Negative	Negative
60	100	5.3	Survived	7.00	14.0	26.0	7.20	16.0	31.0	Negative	Positive† after 3 days' incub.
62	100	6.3	Survived	6.50	13.5	13.6	7.00	15.0	25.8	Negative	Positive† after 3 days' incub.
273*	70	2.5	Survived	7.00	13.0	40.0	7.40	13.0	46.0	Negative	Negative
274*	70	3.2	Survived	6.88	13.0	30.0	7.32	13.5	36.0	Negative	Positive† after 3 days' incub.

*The data on dogs 273 and 274 are reported in detail in a previous paper. They are included in this paper for the purpose of correlation.

†We interpret the fact that these cultures were positive after three days' incubation as evidence that the peritoneal exudate of these animals contained viable spores although the dogs had apparently destroyed the vegetative forms of bacteria. Although no subsequent cultures were taken of peritoneal exudate, the complete recovery of the dogs would indicate that the peritoneal cavity eventually became sterile.

gm. were introduced the dogs sterilized the peritoneal cavity and survived. On this series of animals the lethal amount of cellular elements was in excess of 7 gm. per kilo. of the animal's weight. When less than this amount was introduced, the animals survived but manifested varying degrees of shock. Taking the concentration of blood as an index of the degree of shock, it can be seen that animals subjected to 5 to 6 gm. of cellular elements per kilo. were in a more critical condition than those receiving 2 to 3 gm. per kilo.

In all our studies upon fresh, adult dog liver, the rapid death of the animal has been associated with anaerobic bacterial peritonitis. In our next experiment, an attempt was made to increase the peritoneal resistance of the dog before subjecting the animal to known lethal amounts of fresh, ground dog liver.

TABLE II

THE PROTECTIVE EFFECT OF STEINBERG'S TRAGACANTH VACCINE AGAINST DEATH DUE TO DOG LIVER PERITONITIS

PROCEDURE	DOG	AMOUNT OF FRESH, GROUND, ADULT DOG LIVER PLACED INTRAPERITONEALLY		RESULT
		TOTAL GM.	GM. PER KILO. OF ANIMAL'S WEIGHT	
Unvaccinated animals	199	100	7.00	Died in 15 hr.
	200	100	5.90	Died in 15 hr.
	201	50	3.56	Died in 12 hr.
	202	50	2.60	Died in 15 hr.
Peritoneal immunity increased by intraperitoneal injection of 30 c.c. of Steinberg's tragacanth vaccine 24 hours before the introduction of liver.	203	100	7.60	Survived
	204	100	7.60	Died in 15 hr.
	205	50	3.85	Survived
	206	50	3.33	Died in 72 hr.

Experiment 2.—Eight dogs were used. Four animals were given prophylactic intraperitoneal injections of Steinberg's tragacanth vaccine* and four were untreated. Twenty-four hours later the animals were subjected to intraperitoneal implantations of varying amounts of fresh, ground adult dog liver. Two of the protected animals each received 100 gm. of liver and the remaining 2 each received 50 gm. Two of the unprotected dogs each received 100 gm. of liver and the remaining 2 each received 50 gm. Table II shows the results of the experiment.

Our studies on this phase of the problem are only preliminary but the above experiment indicates that dogs can be protected against death due to liver peritonitis by increasing the peritoneal resistance. We believe this observation supports the concept that rapid death is

*The protective effect of this vaccine has been demonstrated in dogs receiving Steinberg's peritonitis-producing mixture. (Steinberg, B., and Goldblatt, H.: Protection of Peritoneum Against Infection, Surg., Gynec. & Obst. 47: 15, 1933.)

in some manner associated with the growth of dog liver bacteria in the peritoneal cavity. In this preliminary experiment, bacteriologic studies on peritoneal exudate and blood chemical analyses were not attempted.

EXPERIMENTS UPON FRESH, GROUND ADULT DOG LIVER STERILIZED BY AUTOCLAVING

Ellis and Dragstedt,[2] Dvorak,[4] and others have reported that autoclaved fresh, adult dog liver does not kill when placed intraperitoneally. However, if the sterilized liver is infiltrated with dog liver bacteria before it is placed intraperitoneally, it does kill. We likewise reported that autoclaved fresh liver failed to kill unless it was con-

TABLE III

THE PHYSICAL AND CHEMICAL CHANGES IN THE BLOOD OF DOGS SUBJECTED TO INTRAPERITONEAL IMPLANTATION OF FRESH, GROUND, ADULT DOG LIVER STERILIZED BY AUTOCLAVING

BLOOD STUDIES	*DOG 278—WT. 13 KILO.		*DOG 279—WT. 17 KILO.	
	NORMAL	AT 15 HR.	NORMAL	AT 15 HR.
R.B.C.	4,830,000	7,130,000	8,950,000	10,900,000
W.B.C.	12,000	8,650	21,700	8,650
Coagulation time	1′ 30″	40″	1′ 30″	50″
Hemoglobin—gm. per 100 c.c.	12.5	16	14.5	17
CO_2 vol. %	57	†----	53	43
Hematocrit—% cells	47	†----	53	80
Per cent plasma	53	†----	47	20
Plasma volume in c.c.	635	†----	565	220
Blood volume in c.c.	1,200	†----	1,200	1,100
Blood sugar—mg. per 100 c.c.	138	85	74	81
Total N.P.N.—mg. per 100 c.c.	36	62	33	80
Total N. (as protein) gm.	10	12.8	10.6	14.2
Blood chlorides—mg. per 100 c.c.	495	466	495	451

*Dog 278 was given 200 gm. of liver (15.4 gm. per kilo.). Dog 279 was given 100 gm. of liver (5.9 gm. per kilo.).

†Since dog 278 received a large amount of liver intraperitoneally (15.4 gm. per kilo.), we wished to see if he would survive, so we did not do blood volume studies or determine the CO_2 capacity of the blood plasma. These studies entail the removal of 30 c.c. of blood, which is often fatal to dogs suffering from this degree of shock.

taminated.[6] In this series of experiments we have extended our investigations upon this phase of the problem. On numerous occasions we have observed the marked symptoms of shock manifested by dogs subjected to intraperitoneal implantation of fresh liver sterilized by autoclaving. Although the animals survive, they are nevertheless prostrated and acutely ill for a number of hours. The blood pressure is very low, the extremities are cold, and the pulse is weak and thready. Our next experiment was undertaken to ascertain the physical and chemical changes in the blood of dogs subjected to intraperitoneal implantation of fresh, ground adult dog liver sterilized by autoclaving.

Experiment 3.—Livers were removed from sacrificed dogs, ground, and sterilized by autoclaving. The liver substance was introduced

intraperitoneally through a small laparotomy incision with equal volumes of sterile normal saline. Two dogs were used in the experiment. One of the animals received 100 gm. of liver plus 100 c.c. of normal saline, the other 200 gm. plus 200 c.c. of saline. Physical and chemical analyses were made on the blood before the liver was placed intraperitoneally and repeated 15 hours later in the same manner described in a previous publication.[7] The results of the experiment are given in Table III.

The experiment supports the clinical observation that animals subjected to intraperitoneal implantation of this preparation of liver suffer a marked degree of shock. Within a few hours after introducing the liver, both animals were prostrated. Table III shows the marked concentration of blood, loss of plasma volume, and increased total nonprotein nitrogen. We have frequently observed that the loss of a small amount of blood is fatal to such animals. We were not surprised, therefore, when dog 279 died following the removal of 40 c.c. of blood necessary for complete chemical studies. Since we wished to see if dog 278 would survive, only 10 c.c. of blood were removed, and the hematocrit and blood volume determinations were not done. This animal survived even though he was subjected to 200 gm. of liver (15.4 gm. per kilo.). The changes in the blood and the general appearance of the animal indicated a condition of shock comparable to that shown by dog 279 which died following the removal of 40 c.c. of blood.

In Experiment 1, we observed that the cellular elements of fresh ground liver are relatively nontoxic. In our next experiment we attempted to ascertain whether autoclaving the cellular elements of fresh dog liver would influence this result.

Experiment 4.—In this experiment an attempt was made to see if autoclaved cellular elements, infiltrated with a living culture of dog liver bacteria, would cause rapid death when placed intraperitoneally. Seven dogs were used. Each was given autoclaved cellular elements of fresh, adult dog liver intraperitoneally plus equal volumes of sterile normal saline. Each of three of the animals received varying amounts of liver material which had been infiltrated with 1.5 c.c. of a growing culture of dog liver bacteria just prior to its introduction intraperitoneally. The other four dogs were given varying amounts of sterile, autoclaved cellular elements. Since we wished to see if the animals would survive, extensive blood analyses were not attempted. A small sample of blood was removed from each animal for red cell count and hemoglobin estimation before the liver was introduced and additional samples were removed 15 hours later. The results of the experiment are given in Table IV.

TABLE IV

THE EFFECT OF PLACING AUTOCLAVED CELLULAR ELEMENTS OF FRESH, ADULT DOG LIVER INTRAPERITONEALLY AFTER INFILTRATING THE LIVER MATERIAL WITH LIVING CULTURES OF DOG LIVER BACTERIA

DOG	AMOUNT OF AUTOCLAVED CELLULAR ELEMENTS PLACED INTRAPERITONEALLY		BLOOD STUDIES				PERITONEAL EXUDATE REMOVED 15 HR. AFTER INTRODUCTION OF LIVER		RESULT
			NORMAL		AFTER 15 HR.				
	TOTAL GM.	GM. PER KILO.	R.B.C. MILL. PER C.MM.	HB.	R.B.C. MILL. PER C.MM.	HB.	SMEAR	CULTURE	
Autoclaved Cellular Elements Infiltrated With Dog Liver Bacteria									
288	70	4.00	5.37	13.0	7.42	15.0	Negative	Pos. after 3 days' incubation	Survived
289	70	4.40	6.30	12.5	9.11	15.5	Negative	Pos. after 3 days' incubation	Survived
287	100	6.45	6.50	13.0	10.10	17.0	Positive	Pos. in 8 hr.	Died in 9 days
Sterile, Autoclaved Cellular Elements									
290	70	3.2	7.70	14.5	9.45	16.5	Negative	Negative	Survived
291	70	3.7	7.37	13.0	10.47	16.5	Negative	Negative	Survived
292	100	5.3	6.40	15.0	6.37	16.0	Negative	Negative	Survived
293	100	6.6	6.41	15.0	7.84	16.0	Negative	Negative	Survived

All of the animals manifested general symptoms and laboratory signs of shock, but all but one survived. Dog 287 died on the ninth postoperative day with anaerobic bacterial peritonitis. This animal was subjected to 100 gm. of autoclaved cellular elements which had been infiltrated with 1.5 c.c. of a growing culture of dog liver bacteria. Bacteriologic smears made of peritoneal exudate removed from this animal 15 hours, 2 days, 4 days, and 6 days postoperative were all positive for the dog liver anaerobe. Bacteriologic smears taken of samples of peritoneal exudate removed from the other 6 dogs 15 hours after the introduction of liver were negative for vegetative forms of bacteria. However, cultures taken of the peritoneal exudate removed from dogs 288 and 289 were positive for the dog liver anaerobe after 3 days' incubation. We interpret this observation as evidence that the peritoneal exudate of these two animals contained viable spores although the dogs had apparently destroyed the vegetative forms of bacteria.

We find in Table IV that when less than 100 gm. of autoclaved cellular elements were used, two dogs (288 and 289) survived even though the liver preparation was infiltrated with a growing culture of dog liver bacteria. Dog 287, however, was unable to survive 100 gm. of this material, dying in 9 days with peritonitis. The 9-day interval is of interest because of the fact that fresh, raw liver, when given in lethal amounts, always kills in a much shorter time, usually within 24 hours. It appears that autoclaving the liver substance causes decreased toxicity even though the preparation is inoculated with growing cultures of liver bacteria. As an additional check on this observation we carried out Experiment 5.

Experiment 5.—In this experiment we used whole liver ground with equal quantities of salt solution and sterilized by autoclaving. (The connective tissue portions were not removed.) Four dogs were given different amounts of this preparation. In two dogs (307 and 308) the liver preparation was infiltrated with 1.5 c.c. of a growing culture of dog liver bacteria just prior to its introduction intraperitoneally. Samples of blood were removed for red cell counts and hemoglobin determinations before the liver material was introduced, and the analyses repeated 96 hours later. Bacteriologic smears and cultures were taken of samples of peritoneal exudate removed from the animals 1, 2, and 4 days postoperative. The results of the experiment are given in Table V.

A few hours after the intraperitoneal introduction of liver, all four animals showed general signs of severe shock. Red cell counts and hemoglobin determinations made 96 hours after the introduction of liver showed that all the animals were still suffering from shock.

Table V shows that the 2 animals which received sterile, autoclaved liver had no bacteria in the peritoneal cavity, while the 2 animals

TABLE V

THE EFFECT OF PLACING VARYING AMOUNTS OF FRESH, GROUND, AUTOCLAVED ADULT DOG LIVER INTRAPERITONEALLY AFTER INFILTRATING THE LIVER MATERIAL WITH DOG LIVER BACTERIA

DOG	AMOUNT OF AUTOCLAVED LIVER INTRODUCED INTRAPERITONEALLY		BLOOD STUDIES				PERITONEAL EXUDATE REMOVED 1, 2, AND 4 DAYS AFTER THE INTRODUCTION OF LIVER		RESULT
			NORMAL		AFTER 96 HR.				
	TOTAL GM.	GM. PER KILO.	R.B.C. MILL. PER C.MM.	HB.	R.B.C. MILL. PER C.MM.	HB.	SMEAR	CULTURE	
Fresh, Autoclaved Dog Liver Infiltrated With Dog Liver Bacteria									
307	70	4.0	6.35	13.0	8.45	15.5	All pos.	All pos.	Died in 9 days
308	100	6.0	6.47	13.5	9.00	17.0	All pos.	All pos.	Died in 5 days
Fresh, Sterile, Autoclaved Adult Dog Liver									
306	70	4.0	6.80	14.0	9.30	16.5	Negative	Negative	Survived
305	100	7.5	5.80	12.5	8.20	16.0	Negative	Negative	Survived

given the bacterial infiltrated liver substance suffered from bacterial peritonitis. These bacteria were the spore-forming anaerobic species commonly found in adult dog liver. Even though these animals suffered from severe shock associated with an anaerobic bacterial peritonitis, they survived, one for more than 9 and the other for more than 5 days after the intraperitoneal introduction of the inoculated liver substance. This observation confirms the finding reported in Experiment 4, that autoclaved dog liver infiltrated with dog liver bacteria fails to cause death as rapidly as equivalent amounts of unautoclaved raw liver. Both these preparations of liver cause death, and death in each instance is associated with the presence of dog liver bacteria in the peritoneal cavity. To attribute the cause of rapid death in dog liver peritonitis to exotoxins produced by dog liver bacteria seems unreasonable in view of the above observation. It seems more logical to assume that rapid death is caused by toxic substances produced by the action of these bacteria upon raw liver substance.

The experiment also demonstrates that the dog cannot sterilize the peritoneal cavity when ground, autoclaved liver (containing the connective tissue portion) is infiltrated with dog liver bacteria and placed intraperitoneally. (See Table V.) When equivalent amounts of autoclaved cellular elements, infiltrated with dog liver bacteria, were placed intraperitoneally, the dog sterilized the peritoneal cavity and survived. (See Table IV.) We believe that this observation is to be explained on the basis that the finely divided cellular elements permit rapid phagocytosis of any bacterial contaminants.

It appears from the above experiments that neither shock alone, nor shock associated with dog liver bacteria peritonitis, is sufficient to explain the cause of rapid death which occurs when fresh, adult dog liver is placed intraperitoneally. Our experiments have indicated that rapid death is associated in some manner with the action of dog liver bacteria upon fresh liver substance. In order to investigate this concept, we studied the effects of placing incubated liver preparations intraperitoneally.

EXPERIMENTS UPON DIFFERENT PREPARATIONS OF INCUBATED DOG LIVER

Mason, Davidson, and Rastello[1] were the first to report that incubated dog liver was toxic when placed intraperitoneally. Dvorak[4] concluded that the toxicity of incubated dog liver is due to heat labile exotoxins produced by anaerobic bacteria found in adult dog liver. Andrews and Hrdina[8] reported that the toxic factor found in incubated liver belongs to the peptone proteose group and indirectly kills the experimental animal by causing an idiopathic Welch bacillus infection. In our early experiments[6] we presented evidence to show that incubated dog liver is very toxic and rapidly kills, even though the preparation is autoclaved before intraperitoneal injection. Such

autoclaved, lethal preparations of incubated liver could not have contained any heat labile, bacterial exotoxins. Furthermore, by careful bacteriologic technique, we demonstrated that animals given this sterile preparation of liver die without the invasion of the peritoneal cavity by the Welch bacillus or any other bacteria. We observed that the animals died with general symptoms of severe shock.

Our next experiment was undertaken to ascertain the physical and chemical changes in the blood of dogs subjected to intraperitoneal implantation of incubated adult dog liver sterilized by autoclaving. We also wished to contrast these findings with those manifested by dogs subjected to various preparations of fresh, unincubated liver.

Preparation of Incubated Liver.—Livers were removed from sacrificed dogs, using aseptic surgical precautions against contamination. As an added precaution against contamination by extraneous bacteria, the livers were plunged into scalding water until the surfaces were coagulated. The gallbladder, fat, connective tissue, and larger blood vessels were dissected away, and the remaining liver material was passed through a food chopper. The ground liver was divided into 110 gm. portions and placed in 500 c.c. Erlenmeyer flasks together with equal volumes of sterile normal saline solution. The flasks of liver were incubated 3 days at 37½° to 40° C. The flasks of liver were then autoclaved at 15 pounds pressure for 30 minutes and shaken for 50 minutes in a mechanical shaker. This results in a fine division of liver substance and practically all of it strains through six layers of gauze. The strained liver was reautoclaved to insure sterility and placed in the refrigerator until used in the different experiments. The liver substance was handled at all times with sterile technique and every effort was made to prevent contamination by extraneous bacteria.

Experiment 6.—Twelve dogs were used. The animals were starved 24 hours, given a preanesthetic of morphine and atropine, and prepared for aseptic surgery under general ether anesthesia. Each of the animals was subjected to the intraperitoneal implantation of 100 grams of adult dog liver incubated 72 hours and sterilized by autoclaving. The liver material was injected intraperitoneally through a 15 gauge needle pushed through a cautery burn in the abdominal wall. Blood analyses were done on the animals before the liver was injected and repeated some hours later when the animals were at the point of death. The methods used were the same as described in a previous publication.[7] At the time the terminal samples of blood were drawn, 10 c.c. samples of peritoneal exudate were removed for bacteriologic smears and cultures.

All the animals died within 18 hours from the time the liver was introduced. Samples of blood and peritoneal exudate were obtained from 8 of the dogs at the time of, or just before, death occurred. A careful study of smears stained by Gram's method made of peritoneal

exudate showed the presence of occasional gram-negative bacteria with hazy outlines which we believe were killed bacteria introduced with the incubated liver. Only one culture of the eight samples of peritoneal exudate was positive, and we are convinced that most of these animals died with a sterile peritoneal cavity. The changes in the blood were consistent and surprisingly uniform. The results are illustrated by including a typical protocol and table.

PROTOCOL DOG 218

3/27/36

A white, well-nourished, female collie. The animal was starved 24 hours and weighed 31 pounds (14.1 kilos.).

8:30 P.M.—Animal given ¼ gr. morphine sulphate and 1/150 gr. atropine sulphate.

9:20 P.M.—Given general ether anesthesia and prepared for aseptic surgery.

9:30 P.M.—40 c.c. of blood were removed from the jugular vein for physical and chemical analyses.

9:35 P.M.—100 gm. of dog liver, incubated 72 hours and sterilized by autoclaving, were injected intraperitoneally through a cautery burn in the abdominal wall.

9:45 P.M.—Animal returned to the kennels and offered water.

3/28/36

11:30 A.M.—The animal was lying on its side in coma. Breathing was slow and labored, the pulse weak and thready, and the extremities were cold.

11:40 A.M.—40 c.c. of blood were removed from the jugular vein for physical and chemical analyses.

11:42 A.M.—The animal expired. The dog survived the injection of liver 14 hours and died 2 minutes after the removal of 40 c.c. of blood. Ten c.c. of peritoneal exudate were removed for bacteriologic smear and culture and the body was immediately autopsied. Bacteriologic studies showed that the peritoneal exudate contained no living bacteria.

Postmortem Findings.—The peritoneal cavity contained 300 to 500 c.c. of blood-tinged exudate. The intestines were in marked peristaltic contraction. All the peritoneal surfaces were markedly congested and covered with minute pinpoint hemorrhages. The omentum had caught up the major part of the injected liver material. All peritoneal surfaces were covered with a thin, fibrinous exudate. The gallbladder was distended with bile. The temperature of the peritoneal exudate was 106° F. Upon exploring the gastrointestinal tract there was seen a marked hemorrhagic enteritis extending throughout the small bowel, most marked in the duodenum and ileum. There was marked gastritis confined to the fundic portion of the stomach. Upon exploring the thorax the heart was found to be contracted. The lungs were pink with congestion and bled freely from the cut surface.

Immediately after the animals are injected with this preparation of liver they manifest symptoms indicating a severe stimulation of the sympathetic autonomic nervous system. Their pupils are widely dilated; the hair on the back is elevated; the heart rate is profoundly increased and the pulse full and bounding. In several instances, heart arrhythmias and block were observed. This condition lasts for

an hour or more. These animals are very ill and respirations are frequently of the Cheyne-Stokes type. The condition of the animals improves, and 6 to 8 hours following the liver injection they are able to walk about the room. However, they are very weak; the veins are collapsed; and they have a weak and thready pulse. The animals usually pass bloody mucus from the bowel. Their subsequent course is progressively downward. They present all the clinical signs of shock to a marked degree. The physical and chemical changes in the blood of these animals are clearly illustrated in Table VI. There is a marked concentration of the blood associated with a decrease in plasma volume. The blood sugar and CO_2 capacity of the blood plasma are likewise markedly lowered. There is a profound increase in the total nonprotein nitrogen and urea nitrogen of the blood. The

TABLE VI

THE PHYSICAL AND CHEMICAL CHANGES IN THE BLOOD OF DOG 218. THIS ANIMAL WAS INJECTED INTRAPERITONEALLY WITH 100 GM. OF GROUND, ADULT, DOG LIVER, INCUBATED 3 DAYS, AND STERILIZED BY AUTOCLAVING

BLOOD STUDIES	NORMAL	AT DEATH—14 HR.
R.B.C.	8,100,000	12,820,000
W.B.C.	6,850	10,050
Coagulation time	3′ 45″	2 min.
Hemoglobin—gm. per 100 c.c.	16	21
CO_2 vol. %	60	27
Hematocrit—% cells	53	77.6
Per cent plasma	47	24.4
Plasma volume in c.c.	803	328
Blood volume in c.c.	1,710	1,370
Blood sugar—mg. per 100 c.c.	182	67
Total N.P.N.—Mg. per 100 c.c.	35.6	178
Total N. (as protein)—gm. per 100 c.c.	25.9	29.2
Blood chlorides as NaCl—mg. per 100 c.c.	428	388
Urea nitrogen—mg. per 100 c.c.	9.3	45

changes in the blood of these animals are more marked than those seen in dogs subjected to the intraperitoneal implantation of any other preparation of liver we have studied.

The following chart was constructed to contrast the physical and chemical changes in the blood of dogs given lethal preparations of incubated liver sterilized by autoclaving with the changes manifested by dogs given different preparations of unincubated dog liver. The four dogs furnishing the data for this chart presented typical findings and represent observations we have made numerous times.

Dog 274 received 70 gm. of the cellular elements of fresh, raw liver. The animal sterilized the peritoneal cavity and survived.

Dog 279 received 100 gm. of autoclaved, fresh, adult dog liver containing the connective tissue portion. This animal died with a sterile peritoneal cavity following the removal of 40 c.c. of blood necessary for complete chemical analyses.

Dog 294 received 100 gm. of raw, fresh liver containing the connective tissue portion. The dog survived 11½ hours and died with bacterial growth in the peritoneal cavity.

Dog 218 received 100 gm. of ground dog liver, incubated 3 days, and sterilized by autoclaving. The dog survived 14 hours and died with a sterile peritoneal cavity.

Chart I indicates that the blood changes are very marked in those animals receiving lethal preparations of fresh, raw liver. They are even more severe in animals receiving preparations of liver which

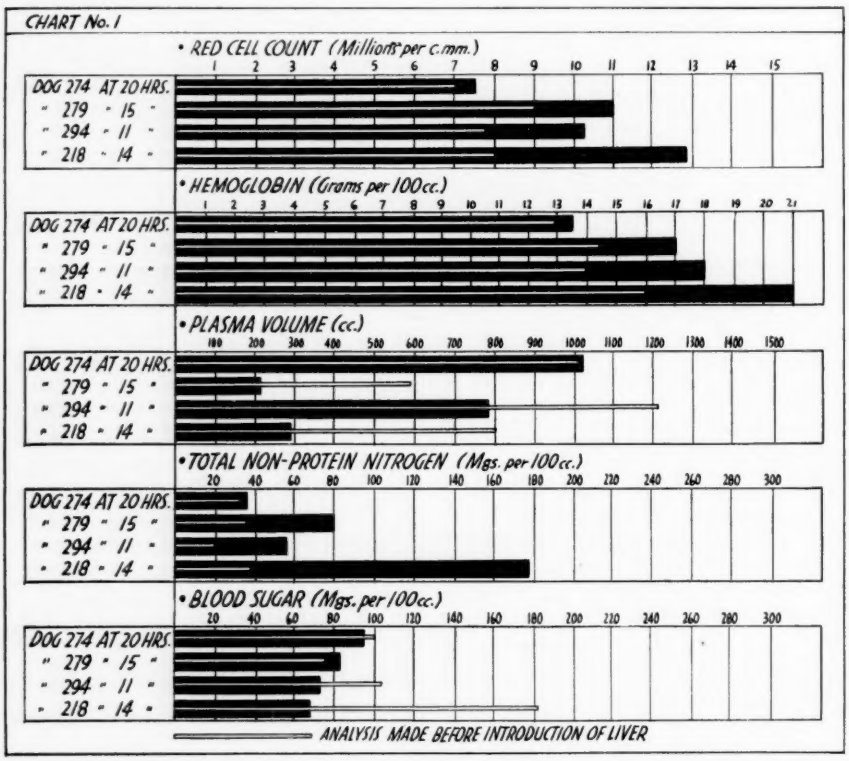

Chart I.—The physical and chemical changes in the blood of dogs subjected to intraperitoneal implantation of various preparations of adult dog liver.

were incubated and sterilized by autoclaving. It is a point of considerable interest that autoclaved fresh liver causes a condition of severe shock. Nevertheless, these animals survive the shock unless large samples of blood are removed during the course of the experiment. Furthermore, our experience shows that complete recovery occurs unless there is an associated bacterial peritonitis. The chart also demonstrates the relative lack of toxicity of preparations from which liver connective tissues have been removed. (See dog 274.)

We wish to emphasize the severe shock and rapid death caused by incubated, autoclaved liver preparations. We have demonstrated

that these animals die with a sterile peritoneal cavity. Furthermore, autoclaving the liver must certainly have destroyed heat labile bacterial exotoxins. It is apparent, therefore, that heat stable, toxic factors are produced by the process of incubation. This represents the rapid digestion of liver, both by the action of dog liver bacteria and by enzymes present in the liver substance. They could conceivably arise either from the bacterial bodies as endotoxins or from byproducts of liver digestion. Finally, the rapid death of the animals may have resulted in part because of the irritating action of incubated liver on peritoneal surfaces, causing congestion and loss of fluids intraperitoneally. Our next experiment was undertaken to ascertain

TABLE VII

THE PHYSICAL AND CHEMICAL CHANGES IN THE BLOOD OF DOGS SUBJECTED TO INTRAPERITONEAL INJECTION OF 100 GM. OF INCUBATED DOG LIVER STERILIZED BY AUTOCLAVING, AND SUBSEQUENTLY TREATED BY INTRAVENOUS ADMINISTRATIONS OF HARTMAN'S SOLUTION AND 5 PER CENT GLUCOSE

*BLOOD STUDIES	DOG 227—SURVIVED 17 HR.		DOG 226—SURVIVED 12 HR.	
	NORMAL	AT 12 HR.	NORMAL	AT 12 HR.
R.B.C.	8,670,000	9,770,000	8,670,000	11,900,000
W.B.C.	8,750	19,350	17,600	11,450
Coagulation time	2 min.	1′ 30″	4 min.	45″
Hemoglobin—gm. per 100 c.c.	11	16	13.5	19
CO_2 vol. %	45	35	50	31
Hematocrit—% cells	49	60	55	81.5
Per cent plasma	51	40	45	18.5
Plasma volume in c.c.	830	252	980	245
Blood volume in c.c.	1,620	630	2,120	1,325
Blood sugar—mg. per 100 c.c.	125	82	169	136
Total N.P.N.—mg. per 100 c.c.	27.6	53	30	54
Total N. (as protein)—gm. per 100 c.c.	21.2	24.3	22	27
Blood chlorides—mg. per 100 c.c.	380	395	390	380
Urea nitrogen—mg. per 100 c.c.	8.3	14.8	8	20

*The terminal samples of blood were removed 12 hours after the injection of liver and 3 hours after the administration of 1,500 c.c. Hartman's solution and 5% glucose. Dog 226 died following the removal of 40 c.c. of blood. The other animal was given an additional 500 c.c. Hartman's solution and 5% glucose and died 5 hours later.

whether the lives of animals subjected to lethal preparations of incubated liver sterilized by autoclaving could be prolonged by accepted methods of shock therapy.

Experiment 7.—Four dogs were injected intraperitoneally with 100 gm. of sterile autoclaved preparations of incubated liver in the same manner as described in Experiment 6. The animals were given intravenous administrations of 500 c.c. Hartman's solution and 5 per cent glucose every 3 hours following the injection of liver until each had received 1,500 c.c. of fluid. The animals revived remarkably with each intravenous medication. From a prostrated stuporous condition they were immediately able to stand on their feet and walk about. However, the improvement was only temporary. Within 3 hours following the administration of fluids the animals were again prostrated

and moribund. None of the dogs survived more than 18 hours. Smears and cultures taken of peritoneal exudate removed from each of the animals, near or at the time of death, were negative. Blood studies were done on two of the dogs before the liver was injected and repeated later as they were dying. The results of these studies are given in Table VII.

The experiment demonstrates that animals injected intraperitoneally with sterile preparations of incubated dog liver die in irreversible shock from which they cannot be saved by intravenous administration of Hartman's solution and 5 per cent glucose. Postmortem examination revealed findings identical to those observed in dogs dying without the administration of intravenous fluids with the exception that the abdominal cavity of these animals contained 1,500 to 2,000 c.c. of blood-tinged exudate. Table VII shows that the changes in the blood are not appreciably altered by the administration of intravenous fluids. The fluids were not retained by the blood stream and passed rapidly into the peritoneal cavity. It is apparent that following the intraperitoneal injection of sterile incubated dog liver the experimental animal rapidly loses the ability of maintaining any fluid balance and dies in irreversible shock.

DISCUSSION AND SUMMARY

The experiments reported in this paper demonstrate the complexity of factors which operate in causing death of the experimental animal subjected to intraperitoneal implantation of liver. We have shown that our experimental results have varied widely according to the character of the liver substance used; whether or not bacteria were present, whether or not we removed the connective tissue from the liver preparations, whether or not the liver was incubated or autoclaved. We have also shown that the peritoneal resistance of the dog has a bearing upon the ability of the animal to survive the intraperitoneal implantation of a given preparation of liver. We have observed that death occurs only when the dog is subjected to liver containing bacteria, or to liver substance upon which the bacteria have been allowed to act in vitro. We believe, therefore, that bacteria which normally inhabit the adult dog's liver are responsible for the rapid death of these animals. We have shown, however, that relatively large quantities of fresh liver containing these bacteria may be placed in the peritoneal cavity of the dog without causing death, providing the connective tissues are removed. Under these conditions the dog is able to render the peritoneum sterile.

Our studies on the physical and chemical changes in the blood have shown that a critical state of shock occurs following the intraperitoneal implantation of a sufficient quantity of any preparation of liver. However, dogs receiving fresh, autoclaved liver in massive

doses (15 gm. per kilo. in one instance) will survive this profound shock, provided the peritoneum remains sterile and provided large samples of blood are not removed during the course of the experiment. Histologic examination of the tissues of these animals shows toxic degenerative changes in parenchymatous organs. We interpret this as evidence that the absorption of liver per se is toxic; but since the animals recover, we do not believe that these toxins are responsible for the rapid death of dogs subjected to intraperitoneal implantation of raw adult dog liver.

Dvorak[4] reported that when dog liver is incubated, a Berkefeld filtrate of the material is fatal when given intravenously to the experimental animal, an observation which might indicate that death was due to bacterial exotoxins formed in the process of incubation. We have repeated Dvorak's experiments and have confirmed his results. However, we observed also that when Berkefeld filtrates were autoclaved and placed intraperitoneally they were equally as toxic as when unautoclaved.

We have repeatedly shown that when fresh, raw liver is incubated and then sterilized by autoclaving it causes rapid death when placed intraperitoneally. The dogs die with profound shock even though the peritoneum remains sterile. We have thus demonstrated that when incubated, autoclaved liver preparations are placed intraperitoneally, death does occur as a result of heat stable toxic substances produced by the incubation of liver; and we are not in sympathy with the concept that death necessarily occurs because of heat labile exotoxins produced by dog liver bacteria. Our experiments demonstrate that rapid death occurs because of toxic substances produced by the action of bacteria upon fresh, raw liver.

Rapid death does not occur when these same bacteria act upon autoclaved, fresh liver in the peritoneal cavity. Dogs which receive autoclaved liver inoculated with living cultures of dog liver bacteria can live for several days with bacteria growing in the peritoneal cavity. Although the dogs eventually die, their death is not the same as that of animals given fresh, raw liver.

We have investigated the nature of the toxins produced by the incubation of dog liver in vitro. We believe that these toxic substances are merely the protein split products of liver digestion in the presence of putrefactive bacteria, namely, peptones, proteoses, and putrefactive amines. Pharmacologically, we have demonstrated the presence of tyramine, histamine-like substances, and various others. The details of this study are being reported in another publication. We further believe that all these toxic substances are rapidly produced by the action of dog liver bacteria upon the autolyzing liver substance either in vivo or in vitro and are probably the toxins responsible for the rapid death of dogs subjected to liver peritonitis.

We have further observed that the intraperitoneal absorption of liver proteins which have undergone no bacterial digestion causes a critical state of shock associated with parenchymatous degeneration of the liver, kidneys, and adrenal glands, and we believe that these factors also contribute to the rapid death of these animals.

We are aware that these studies may seem to have little clinical significance. However, if human livers harbor bacteria, it is conceivable that they may be factors in the toxemias and shock associated with liver necrosis. Furthermore, there is an accumulation of evidence that human muscles, or the deep lymphatic spaces, may at times harbor bacteria. In this event, our experimental observations upon the rôle played by bacteria in causing rapid death in liver peritonitis may offer a possible explanation for the fulminant toxemias associated with shock, which sometimes occur immediately following traumatic surgical procedures in human subjects.

We wish to express our appreciation to Dr. W. D. Gatch, under whose supervision our investigations originated. Dr. Lynn Arbogast and Dr. Ralph Gettlefinger rendered valuable technical assistance.

REFERENCES

1. Mason, E. C., Davidson, E. C., Matthew, C. W., and Rastello, P. B.: A Study of Tissue Autolysis In Vivo, J. Lab. & Clin. Med. **10**: 622, 1925.
   Mason, E. C., Davidson, E. C., and Rastello, P. B.: Study of Tissue Autolysis In Vivo: Pharmacological Study of Toxic Material, Ibid. **10**: 906, 1925.
2. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis In Vivo, Arch. Surg. **20**: 8, 1930.
3. Andrews, E., Rewbridge, A. G., and Hrdina, L.: Causations of Bacillus Welchii Infections in Dogs by the Injection of Sterile Liver Extracts or Bile Salts, Surg., Gynec. & Obst. **53**: 176, 1931.
4. Dvorak, H. J.: Liver Autolysis in the Peritoneal Cavity of the Dog, Proc. Soc. Exper. Biol. & Med. **29**: 431, 1932.
5. Trusler, H. M., and Reeves, J. R.: The Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis, Arch. Surg. **28**: 479, 1934.
6. Trusler, H. M., Reeves, J. R., and Martin, H. E.: Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis: A Bacteriological Study of Peritoneal Exudates, Arch. Surg. **30**: 371, 1935.
7. Trusler, H. M., and Martin, H. E.: The Cause of Death in Liver Peritonitis: Blood Chemistry Findings in Dogs Subjected to Intraperitoneal Implantation of Fresh, Ground, Adult Dog Liver, SURGERY **1**: 243, 1937.
8. Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, Surg., Gynec. & Obst. **52**: 61, 1931.

RELATION OF DUODENAL REGURGITATION TO THE DEVELOPMENT OF JEJUNAL ULCERS

HERBERT C. MAIER, M.D., NEW YORK, N. Y., AND ABRAHAM GROSSMAN, M.D., CHICAGO, ILL.

(From the Surgical Pathological Laboratory of the College of Physicians and Surgeons, Columbia University, and the Surgical Department of the Presbyterian Hospital)

THIS paper is confined to a consideration of postoperative jejunal ulcer; no consideration will be given to the rare primary jejunal ulcer which is probably of different pathogenesis. The terms postoperative jejunal ulcer and gastrojejunal ulcer seem preferable to the term marginal ulcer, because many of the ulcers are opposite the gastrojejunostomy stoma and do not actually extend to the line of the junction of the gastric and jejunal mucosa. Moreover, some of the large jejunal ulcers which do extend to the line of anastomosis possibly originate a short distance away. In this paper, the term duodenal regurgitation refers to any drainage of duodenal contents back into the stomach; the term is not restricted to reflux through the pylorus.

During the past fifteen years much experimental work has been done on peptic ulcer, and most of this work has been on dogs. Apparently, spontaneous chronic gastric and duodenal ulcers occur but rarely in dogs. Acute ulcerations occur with moderate frequency, but these lesions differ in many ways from the usual type of peptic ulcer seen in man, and investigation of these is of little benefit in helping to discover the etiology of chronic peptic ulcer. It might be mentioned, however, that acute infections induced in animals under some circumstances produce acute ulceration of the stomach or duodenum, especially the latter, and sometimes with perforation. Similarly in man, one occasionally sees an acute ulceration with perforation of the duodenum at autopsy in a patient with a fulminating infection or brain lesion. With few exceptions, workers have been unable to produce chronic peptic ulcers in the stomach and duodenum of the dog. Gastric ulcers have been occasionally produced by preventing the regurgitation of duodenal contents into the stomach with simultaneous feeding of hydrochloric acid. One of the few methods by which chronic ulcers resembling peptic ulcers in man can be produced with regularity involves the principle of having gastric juice come in contact with jejunal mucosa unprotected by alkaline duodenal contents. This is the so-called surgical duodenal drainage, familiarly known as the Mann-Williamson[1] operation (Fig. 1). In this operation the pylorus is severed and the duodenal end inverted,

Received for publication, February 16, 1937.

The jejunum is severed just beyond the duodenojejunal junction, and the proximal cut end of jejunum is anastomosed to the ileum while the distal cut end of jejunum is anastomosed to the pyloric end of the stomach. By this means, all the duodenal contents are shunted into the lower ileum, and the gastric juice is emptied into a jejunum which can receive no duodenal contents. After this operation, ulcers form in the jejunum close to the gastrojejunostomy stoma. It has been shown by a large number of workers that this procedure is a most reliable way of consistently producing ulcers which are similar to chronic peptic ulcers in man; whereas, these experimentally produced ulcers are very similar to gastrojejunal ulcers in man, there are important points of difference from gastric and duodenal ulcers. Therefore, it is questionable to what extent results obtained from the investigation of these ex-

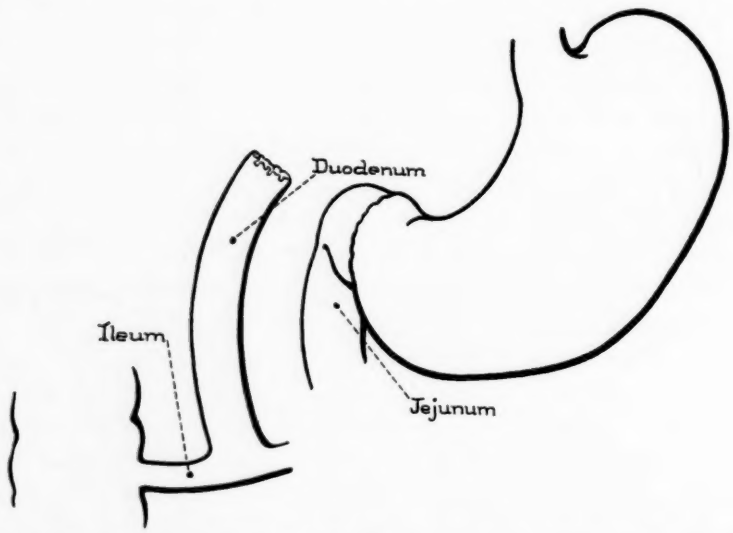

Fig. 1.—Surgical duodenal drainage into the lower ileum (Mann-Williamson operation).

perimental ulcers may be applied to the question of etiology of gastric and duodenal ulcers in man; however, there is much similarity between these ulcers and gastrojejunal ulcers.

Experimentation up to the present time indicates that one of the important etiologic factors in the production of peptic ulcers, and especially of gastrojejunal ulcers, is the action of the gastric juices. The question of whether the acid itself is the main factor or whether the pepsin in the gastric juice is also an important factor, cannot be regarded as settled at the present time. There is rather convincing evidence, however, that other factors, such as muscle spasm, stenosis, mechanical trauma, and nervous reflexes associated with hyperacidity, play an important part. In addition to this, and especially in the consideration of gastrojejunal ulcers, the increasing vulnerability of the intestinal mu-

cosa to gastric juice as the distance from the pylorus increases must be borne in mind. This fact has been convincingly shown by the experimental work of McMaster[2] and others. Those cases in humans where by mistake gastroileostomy was performed instead of gastrojejunostomy, with the rapid subsequent development of an ulcer are further evidence of this fact. Therefore, one principle which must be borne in mind in performing an operation for peptic ulcer is that, other things being equal, the more distal the loop of jejunum which is used for the gastrojejunostomy, the more likely jejunal ulceration is to occur. This is especially important to consider where complicated secondary operations may be required for jejunal ulceration.

In the various surgical procedures used in the treatment of peptic ulcer, there are several objectives which are sought after; and their attainment is considered as increasing the likelihood that the surgical procedure will give a good end-result. The principle objectives are (1) reduction of the acidity, and (2) rapid emptying of the stomach. In speaking of the effect that a particular type of surgical operation has on the acidity, one must be careful to be specific as to what is meant. One usually analyzes the gastric contents and refers to these values. However, in considering the question of acidity in relation to the etiology of gastrojejunal ulcer formation one must remember that a reduction in gastric acidity does not mean a corresponding change in the reaction of the jejunal contents near the gastrojejunal stoma. The pH of the contents in the efferent loop of a gastroenterostomy is the net result of the pH of the gastric contents discharged through the gastroenterostomy stoma and the pH of the jejunal contents itself. In the Mann-Williamson type of surgical duodenal drainage which has been widely used experimentally to produce jejunal ulcers, the important fact is not the acidity of the gastric contents itself, but the absence of alkaline juices on the jejunal side of the anastomosis, except for the slight jejunal secretion. As a result, no appreciable further neutralization of the gastric contents occurs in the upper jejunum. Although by this operation the gastric acidity is somewhat elevated, the change is not as marked as one might think. Examination of the jejunal contents, however, shows a considerable change to the acid side postoperatively.[3] The same principle applies, to some extent at least, to the various surgical procedures used in the treatment of gastric and duodenal ulcer. In a Polya type of resection, for instance, if most of the duodenal contents coming up the afferent loop go back through the gastrojejunostomy stoma into the resected stomach and mix with the gastric contents, the analysis of the gastric contents may show a low acidity; but this acidity may be almost the same as that in the efferent limb of the gastrojejunostomy, since in this instance there is little alkaline juice which is being shunted directly from the afferent to efferent loop of the gastrojejunostomy. In another

case of Polya resection, because of a different mechanical arrangement, a smaller percentage of the duodenal juices passing along the afferent loop might be shunted back into the stomach, and although the gastric acidity itself might be higher than in our previous case, the contents of the efferent jejunal loop actually might be more alkaline. So one must bear in mind that analysis of the gastric acidity does not indicate the pH of the contents of the efferent loop where jejunal ulcers are likely to form.

There has been considerable difference of opinion concerning the relative importance of the reflux of duodenal contents into the stomach in reducing gastric acidity. By some it is considered the chief mechanism by which the gastric acidity is reduced in the later stages of digestion of a meal in the stomach; whereas, others believe its importance is greatly exaggerated. Furthermore, it must be remembered that some constituents of the duodenal contents are a slight stimulus to gastric secretion. However, there can be no doubt whatsoever concerning the importance of the duodenal contents in neutralizing and diluting the gastric chyme after it leaves the stomach. In the case of some of the operations used in the treatment of peptic ulcer, the regurgitation of the alkaline intestinal contents into the stomach is regarded as one of the important points to be achieved; in gastroenterostomy, for example. Furthermore, there is much evidence that considerable reflux does occur.[4] In partial gastrectomy the emphasis is more on the reduction of the acid secretion of the stomach and the rapid drainage of gastric contents than on regurgitation of duodenal secretions.

Since duodenal regurgitation is considered desirable, it is quite surprising to note that McCann[5] reports the development of jejunal ulcers in approximately 80 per cent of twenty-six dogs with gastrointestinal anastomoses through which there was complete regurgitation of duodenal contents into the fundus of the stomach. In fact, he came to the conclusion that jejunal ulcers could be produced as readily by diverting the duodenal contents into the stomach as by draining them into the lower ileum. Furthermore, he did preoperative and postoperative gastric analyses using a test meal and thought that the type of acidity curve was similar. Examination of these curves, however, shows that in the dogs in which the duodenal contents were diverted into the lower ileum, the acidity remained at a high level for a longer time postoperatively. On the other hand, in the cases in which the duodenal contents were drained back into the stomach, there was a slightly lower acidity than in the preoperative analyses.

As far as we have been able to ascertain, this work of McCann has not been repeated by other investigators. However, an arrangement similar to McCann's, with the exception that the duodenal contents were shunted

into the prepyloric portion of the stomach instead of the fundus, has been used in experimentation by at least three workers.[6, 7, 8] They used a total of thirty-seven dogs and obtained only two jejunal ulcers. The question naturally arises whether this difference in the site of the entrance of the duodenal contents into the stomach, with resultant difference in the thoroughness of mixing of the gastric and duodenal juices, could be responsible for the difference in the results. Therefore, it seemed worth while to repeat McCann's experiments with certain modifications. There are some theoretical and practical considerations of considerable importance that these experimental observations bring to one's mind. If it were true that complete duodenal regurgitation were associated with a high incidence of jejunal ulcer and little change in gastric acidity, it would be of considerable clinical importance, because ordinarily duodenal

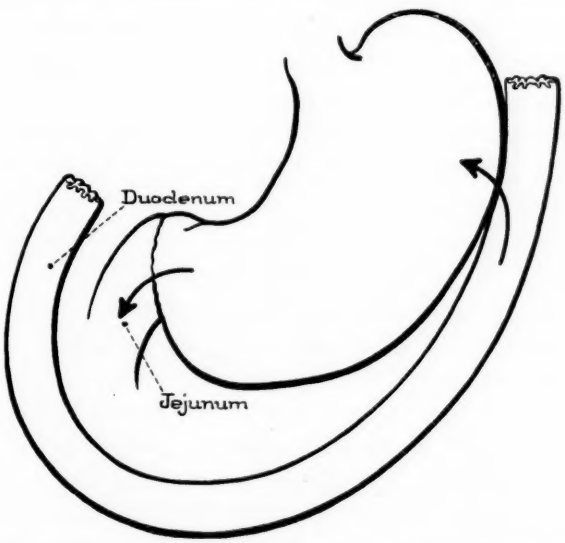

Fig. 2.—Surgical duodenal drainage into the fundus of the stomach.

regurgitation is considered very desirable. In fact, recently there have been proposals of new operations for peptic ulcer based on the principle that the more complete the degree of regurgitation of the duodenal contents, the better the results would be and the less the likelihood of postoperative jejunal ulcer.

EXPERIMENTAL DATA

Two groups of experiments were carried out. In one group, a procedure similar to that used by McCann was employed (Fig. 2). Dogs were used as the experimental animals. All operations were performed under ether anesthesia and with the usual aseptic precautions. The abdomen was opened through an upper right rectus incision. The duodenum was severed just beyond the pylorus and the duodenal stump inverted. The jejunum was then divided as short a distance as practical beyond the duodenojejunal junction. The proximal cut end of jejunum was anastomosed to the fundus of the stomach by a side-to-side anastomosis. This was done as far

to the left side of the stomach as was mechanically possible. The distal cut end of the jejunum was anastomosed to the pyloric end of the stomach end-to-end. Before making this anastomosis, the pyloric end of the stomach was cut at an angle; the same was done to the end of the jejunum. This was done in order to obtain a larger stoma and also to eliminate to some extent the sphincteric action of the pyloric muscle so that gastric emptying would not be interfered with. No appreciable portion of the stomach was removed, however. Absorbable suture material was used for all anastomoses. After the immediate postoperative period, the animals were fed on the usual kennel diet.

The animals were permitted to live until they were moribund or died. Seven dogs survived the operation from one and one-half to seven months; most of them lived over six months. In addition, several dogs died within a month of operation; none of these had jejunal ulcers. All the dogs showed progressive loss of weight and strength, in spite of the fact that their appetites were good. Their stools were large and often foul smelling; this was considered to be due to a partial inability to utilize the ingested food. Vomiting was rare. All of the animals became very anemic. Of the seven dogs which lived sufficiently long to be considered for purposes of the experiment, six died apparently of cachexia due to nutritional disturbance. Part of this nutritional disturbance may be due to the fact that in the case of these animals some of the digestive enzymes, such as trypsin, do not have a medium of the proper pH for optimum action. There were no other findings in these animals at autopsy except congestion of the jejunum. Only one dog had jejunal ulceration. This dog had two rather large jejunal ulcers close to the gastrojejunostomy stoma; one of these, just opposite the stoma, had perforated. This animal was the only one to show some dilatation of the stomach. There were also submucosal petechial hemorrhages in the greater part of the jejunum. None of these seven dogs showed any appreciable degree of duodenal dilatation, but in some of the dogs which died shortly after operation and which are not included in the seven of the above group, definite duodenal dilatation was present. These latter dogs vomited considerably postoperatively. In two instances in which this duodenal dilatation and stasis was marked, it was the only obvious cause of death.

Analysis of the gastric contents after stimulation by the injection of histamine was carried out in the case of several animals both preoperatively and postoperatively. In each instance there was a considerable reduction in acidity after operation. Also, in the case of several of the animals, studies of the ability of the stomach to neutralize acid were made before and after operation. The following procedure was employed: After analysis of the fasting gastric contents, 200 c.c. of tenth normal hydrochloric acid were introduced into the stomach. A 10 c.c. sample was removed immediately after introduction and then at fifteen-minute intervals for one and one-half hours or until no more

specimens could be obtained. A considerable increase in the ability to neutralize acid was noted in all cases after complete duodenal regurgitation had been produced by operation.

A second group of experiments were carried out. In this group, a similar surgical procedure was performed, except that about one-half of the stomach was resected in addition. (Fig. 3.) The pylorus was severed, and the duodenal end inverted. The distal half of the stomach was resected; the jejunum was severed just beyond the duodenojejunal junction, and the proximal cut end of the jejunum implanted into the fundus of the stomach side-to-side. The distal cut end of jejunum was anastomosed to the resected end of the stomach end-to-side. This resulted in complete duodenal regurgitation in a resected stomach.

Five dogs survived this operation from two to five months. All the dogs showed changes similar to those seen in the previous group. At

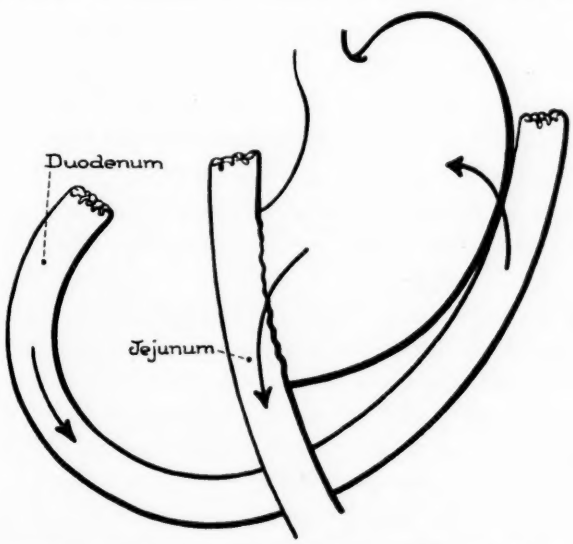

Fig. 3.—Surgical duodenal drainage into the partly resected stomach.

autopsy, only one dog had a jejunal ulcer; this ulcer had perforated. The other dogs died apparently of cachexia from nutritional disturbance.

Gastric analysis in this group showed a somewhat lower acidity postoperatively with histamine stimulation than in the previous group. In one instance only was there anacidity. These animals were able to neutralize acid very rapidly.

DISCUSSION

It is not entirely obvious why we obtained such a markedly different incidence of jejunal ulcers from that which McCann reported. It is probably not due to the length of time which the animals survived, because McCann states that most of his dogs developed ulcers within one to three months after operation, while most of our animals survived about six months. If the difference in frequency of jejunal ulceration

were due to the fact that McCann etherized some of the dogs when they refused food and lost weight; whereas, we waited until the dogs died, then probably the ulcers in his dogs were not really chronic in character, although we saw no evidence of scarring of the jejunum at autopsy. The site of entrance of the duodenal contents into the stomach might be a factor, but we implanted the duodenal end of the severed jejunum as far from the pyloric end of the stomach as possible. The size of the gastrojejunostomy stoma at the outlet of the stomach and the fact that we cut the pyloric muscle in such a way as to reduce the sphincteric action of the pylorus might well be the explanation for the difference of our results. Ivy and Fauley[8] and Steinberg and Proffit[9] have shown the great diminution in the incidence of jejunal ulceration in dogs when an anastomosis with a large stoma is made. Furthermore, McCann mentions definite delay in gastric emptying, probably due to stenosis at the gastrojejunostomy stoma; whereas, in our animals gastric emptying was more rapid than before operation. The adequacy of the blood supply in the area where the ulcers form, the types of dogs used, and their diets might all be factors, but cannot be evaluated.

The relationship between the nutritional status of the animal and the development of experimental jejunal ulcers is an important factor to consider. Flood and Mullins[10] recently considered this point and studied the nutritional disturbances in dogs after the Mann-Williamson surgical duodenal drainage. Our dogs showed similar changes, although the changes occurred more gradually. However, a difference in nutritional status does not seem to be the explanation for the difference between our results and those reported by McCann, because our dogs apparently showed the greater evidence of nutritional difficulties, and yet our incidence of ulcer was much less.

Even though we obtained a much lower incidence of jejunal ulceration than McCann reported, one may conclude that in spite of regurgitation of duodenal contents into the stomach with resultant diminution in the acidity of the gastric contents, jejunal ulcers may form, because the jejunum may thereby be exposed to a relatively more acid secretion. This is even true when we have a partial gastrectomy in addition to complete duodenal regurgitation. Apparently there is a mechanism by which the stomach, to some extent at least, controls the acidity of the contents ejected from the stomach. The alkaline duodenal juices to some extent are analogous to added alkaline by mouth, and produce a somewhat similar response of gastric secretion; both cause some secretion of acid but not a sufficient amount to neutralize completely the alkali. However, part of the duodenal alkali is lost, so to speak, as far as being available for neutralization on the distal side of the pylorus. Therefore, the end-result is that the jejunal mucosa is exposed to a more acid contents than if no regurgitation had occurred. To corroborate these points the report of Schmilinsky[11] is interesting. He operated

upon three cases of jejunal ulcer following gastroenterostomy and performed an operation by which there was forced regurgitation of all duodenal contents back into the stomach. One patient died postoperatively; one died one year later of a new perforated jejunal ulcer; while the third had much epigastric distress, a so-called gastritis, and developed dilatation of the duodenal loop. The operation was also carried out on five cases of duodenal ulcer. Several of these had gastrointestinal symptoms of considerable severity after the operation. They also seemed to develop a form of gastritis. An anacidity was not always obtained. Schmilinsky concludes that, whereas, the stomach is physiologically adapted to deal with a small amount of duodenal contents, it is not intended to handle a large amount.

That jejunal ulcers will occur with the same frequency whether all or none of the duodenal contents is shunted back into the stomach, as McCann believed, does not seem to be true. All workers who have used the Mann-Williamson operation report a much higher incidence of jejunal ulcers than we obtained in our experiments. In fact, Owings and Smith[12] report the healing of a certain percentage of jejunal ulcers produced by surgical duodenal drainage when the duodenal contents are later shunted back into the stomach.

SUMMARY

In a consideration of the rôle of acidity in the production of jejunal ulcers, the analysis of the gastric contents is a very unreliable guide.

Whereas the more the regurgitation of intestinal contents into the stomach after a gastroenterostomy or gastric resection, the lower the resultant gastric acidity, this regurgitation will not lower the acidity in the efferent loop of the jejunum. Therefore, although the regurgitation lessens the chances of further trouble with the gastric or duodenal ulcer, it does not diminish, but in fact may increase the chances of developing a jejunal ulcer.

Mechanical factors, such as kinks, stenosis, and the muscular spasm, also play a rôle in jejunal ulcer formation.

The details of the mechanical arrangement in each individual case will be an important factor in determining the amount of duodenal contents regurgitated into the stomach after a gastric operation and hence may influence the chances of jejunal ulcer formation.

We have been unable to corroborate McCann's finding of a very high incidence of jejunal ulcer in dogs after drainage of the duodenal contents into the fundus of the stomach. The difference in our results is due probably to the larger gastrojejunostomy stoma which we employed.

Considerable digestive disturbance may result from complete duodenal regurgitation.

REFERENCES

1. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**: 409, 1923.
2. McMaster, P. E.: Effects of Diverting Gastric Contents to Lower Intestinal Levels, Arch. Surg. **28**: 825, 1934.
3. Wu, P. P. T.: Reactions of Contents of Jejunum and Experimental Production of Peptic Ulcer, Arch. Surg. **30**: 557, 1935.
4. Wilhelmj, C. M., Henrich, L. C., and Hill, F. C.: Influence of Duodenal Secretions on Acid Gastric Contents, Am. J. Physiol. **111**: 293, 1935.
5. McCann, J. C.: Experimental Peptic Ulcer, Arch. Surg. **19**: 600, 1929.
6. Graves, A. M.: Combined and Separate Effects of Bile, Pancreatic Secretion, and Trauma in Experimental Peptic Ulcer, Arch. Surg. **30**: 833, 1935.
7. Weiss, A. G., Graves, A., and Curiaran, G.: La dérivation intragastrique des sucs alcalins duodenaux, Comp. rend. Soc. de biol. **109**: 916, 1932.
8. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining Chronicity of Ulcers in Stomach and Upper Intestine; Susceptibility of Jejunum to Ulcer Formation; Effect of Diet on Healing of Acute Gastric Ulcer, Am. J. Surg. **11**: 531, 1931.
9. Steinberg, M. E., and Proffit, J. C.: The Etiology of Postoperative Peptic Ulcer, Arch. Surg. **25**: 819, 1932.
10. Flood, C. A., and Mullins, C. R.: Experimental Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **3**: 249, 1936.
11. Schmilinsky, H.: Zentralbl. f. Chir. **45**: 417, 1918; and Personal Communication, 1935.
12. Owings, J. C., and Smith, I. H.: Experimental Production and Cure of Jejunal Ulcers, Proc. Soc. Exper. Biol. & Med. **29**: 832, 1932.

Editorials

The Training of the Surgeon

BARON BOYER'S statement, made early in the nineteenth century, that surgery had reached the greatest heights to which it could ever attain, is another example of how easily the surgical prognosticator may be led astray. The art of surgery and the science upon which it is built are constantly changing and, as a result of this, the preparation of young men interested in a career in surgery must also change.

The training of the barber surgeons was in large part based upon a knowledge of anatomy. It remained for John Hunter to give surgery a firm and lasting foundation in pathologic anatomy. With the development of the aseptic discipline, surgical therapy was revolutionized and in the last quarter of the nineteenth century more was accomplished to place surgery on a firm basis than in all the years which had gone before. It was during this period that symptomatology was correlated with the morbid anatomy of the living patient and not with the end-results of pathologic processes, as observed at the autopsy table.

The art and science of surgery was in large part developing during this period because of the expansion which was taking place primarily in bacteriology, but also in physiology, physiologic chemistry, and pathology. While it was previously considered sufficient for the surgeon to have a background in anatomy and pathology, it has become equally important that he have had a good basic training in these other sciences.

Since the ultimate aim of surgery is to restore function, it is only by the surgeon's ability to do this with increasing effectiveness that we can maintain a dynamic art. To restore function the surgeon must possess an intimate knowledge of normal function, and the methods by which pathologic processes lead to changes in function. Thus, an intimate, working knowledge of what are unfortunately called the preclinical sciences is of the greatest importance to the surgical specialist as well as to the general surgeon.

It is training of this type which has resulted in the rapid developments of neurosurgery, thoracic surgery, and the surgery of the cardiovascular system. It is upon the firm foundation of physiology in its broadest aspects that the great advances in the pre- and postoperative treatment of the handicapped patient have been developed.

Many of the ablest minds in the surgical profession have been keen observers. They have, in many instances without knowing it, made a laboratory of the bedside and the operating table, and these can be just as much of a laboratory as the purely experimental workshop.

It has, furthermore, been stated that a rigid discipline in the basic sciences may be necessary for the neophyte who is preparing himself for an academic career in surgery. I cannot see that the training need or should be any different for the surgeon who does not have the oportunity to teach in our medical schools. He will, in all probability, train young men, and as a group the surgical practitioners will be entrusted with a larger number of lives. The surgical practitioner must not only have a working background in the basic sciences, but he must provide himself with the means of keeping in contact with the important advances in these subjects, as they relate to the art and science of surgery.

There are still many surgeons who express their belief that this foundation in the basic medical sciences as a part of the training of the surgeon is overemphasized, with the result that the young surgeon is becoming too scientific; that the ability to use his fingers dexterously is the sine qua non of a student's training. A review of the publications of some of these men shows that often they attempt to utilize the developments of the basic sciences to clothe their own contributions, a lack of consistency in the point of view which they take.

It would be folly to state that the technical aspects of surgery had reached their fullest development, but it is, I believe, a just prognostication to state that the improvements in the end-results of surgical therapy will come from an ever enlarging knowledge of the processes involved in maintaining normal function, and our ability to understand the mechanism involved in alteration from the normal.

As long as we refuse to accept this point of view, the training of the surgeon will be distorted, and as Buckle has said, the philosophy of any subject is not at its center but on the periphery where it impinges on all the other sciences.

The training of young men interested in a surgical career should be based upon more than a foundation in anatomy, pathology, and the technical aspects of surgical maneuvers. It should, in part, include training in the other basic sciences. This will bring surgical knowledge from the inner circle to the periphery where the surgeon will meet and interpret the normal and abnormal processes of living tissues, and from such a contact developments cannot help but come.

—*I. S. Ravdin, M.D.*
Philadelphia, Pa.

Training the Young Surgeon

THE proper training of the young surgeon is being given a great deal of justified attention, and perhaps the most important recent step is in the formation of the American Board of Surgery for the certification of those properly qualified. In most instances this is going to mean, for the young group, a residency or its equivalent.

In the effort to improve the standard of surgery, a great step forward has been taken. A definite minimum period of hospital training for those who wish to be certified has been established and this, with the hospital standardization of the present and that to come, should insure a favorable circle of better trained men making better institutions and better institutions making better trained men.

We have established standards of premedical education, medical education, hospital training, and we have specified that there must be two years of surgery added to those spent in hospitals (with a fourth year residency). It seems that it would be helpful for those in authority to further aid by providing, as far as possible, positions and work for this young group of well-trained men, thereby aiding them, the hospitals, the surgical dispensaries, and the medical schools.

The American Board of Surgery demands a four-year hospital training and "an additional period of not less than two years of study or practice in surgery." This last regulation is necessarily a more or less loose one, in that a percentage of men will form attachments that are of little value, a marking of time only, while others will obtain positions giving them excellent training and experience. Thus it is seen that, with all the care and thought given, there is, in most cases, a weak link in the chain; namely, the years following a residency or other hospital training. In our present system there is, from graduation on, a step-by-step advance in knowledge and opportunity to the crescendo of the year as resident surgeon when a large experience is obtained; then there is a sharp diminuendo, during which many tangles can be straightened out of the skein, much reading done, notes, records, and ideas clarified and amplified, but the hands are more or less idle.

How to help bridge this gap is a pertinent current question. The need of surgical experience on the part of the young surgeon and the problem of extensive and increasing dispensary and free ward services should be subject to adjustment mutually beneficial. Naturally no hard and fast rules applicable to all hospitals can be established. A large hospital with a five-, six-, or seven-year residency is different from one with a four-year residency. Hospitals affiliated with medical schools are in a somewhat different position from those not so connected, but the discussion of any plan may direct some attention to, and help strengthen, this weak period in the present general scheme until further study crystallizes a more universally acceptable plan.

It may be that the next few decades will see the development of hospitals for postgraduate training different from those now available. (The Roman Catholic Archbishop of Baltimore has at his disposal a fund of $5,000,000 which he hopes to let grow for an indefinite number of years; and, when it is sufficiently large, he has in mind the establishment of a hospital planned to cover some of the problems outlined above.)

For some years we have had at the hospital* with which I am connected, a plan that is not without serious faults but which has advantages that may be worth considering. Our hospital, a general one of 250 beds, is connected with the University of Maryland School of Medicine and is used for teaching one-half of the senior class and for some of the junior classwork. The chief surgeon and the staff of attending surgeons, including the specialists, attend the wards and do the teaching. The arrangement of the work of the senior surgeons does not interest us here. The plan for the younger men may perhaps best be traced from below upward. If the resident surgeon is a native of the city or if he decides to remain and desires to become connected with the hospital, he is required to work in the dispensary and do dispensary teaching. If he continues to be earnest, interested and deserving, and if he confines his work to surgery, an effort is made to give him a connection with the ward work. This consists at first of a night service; that is, for one or more nights a week he is on call from 7 P.M. to 7 A.M., to be responsible, with the resident, for the ward cases that come in as emergencies, a senior surgeon being consulted, if necessary. Naturally this gives him a limited type of work, omits, in the main, elective cases, but gives him difficult diagnostic problems, all types of acute conditions, traumatic cases, etc.; but more important, it gives him a connection with, and interest in, the ward work. Further, it puts him in line for promotion. The next older group gets a summer service and looks after the wards between the school sessions. From these two groups the teaching staff is recruited, each regular teacher picking one of the most likely of the younger men as a substitute in case he cannot meet a class. In this way, the younger group is kept interested in the dispensary work, the ward work, and the teaching, at the same time not themselves becoming stagnated. Each substitute has to be prepared to give a clinic or ward class on short notice; he must be ready not only to discuss a case and operate, but he must have dry clinics prepared.

One of the first criticisms will, no doubt, be that this plan interferes with the resident's work. That might be more largely the case in a hospital with five-, six-, or seven-year residency, but it does not hold so true with a four-year man, who is not permitted to do much operating until the latter half of his residency. When he finishes his term, he has seen a great deal and has had a large experience, with from 200 to 300 major operations, but most of his operating comes in the last part of his term.

The residency begins and ends September 1; whereas, the other members of the house staff change July 1. This is done for two chief reasons:

A. Because it allows the outgoing resident the summer months to break in the rotating internes and the assistants, though these latter are usually rotators who have been promoted and know the ropes.

*Mercy Hospital, Baltimore, Md.

B. It permits the resident to have two months at the end of his training period when no clinics are being held and during which he gets a large amount of material. It is customary for the young attending man to let the resident do the operating, but he is there, he sees the case, gets the experience, discusses it with the resident, and it is helpful to both and safer for the patient than having the resident unsupervised.

This comes in slight conflict with the rule of the American Board of Surgery requiring "adequate operative experience in which the candidate has assumed the whole responsibility ————." Perhaps there is room here for argument, with the patient having an advocate.

A second objection might be that the supply and demand might not balance. The plan is flexible to a considerable degree. At present we have seven men on night duty—no hardship on any one. The nights could be divided among any less number. For instance, giving three men two nights and the newest recruit one, or giving five men a night each and the sixth two nights, etc.

If appropriate applicants are scarce from one's own ex-residents, outside talent is called upon. If there are too many applicants, it is a survival of the fittest. The attrition of the specialties, increasing private work, indifference, inability to teach, will eliminate a percentage.

A third argument might be that the young attending surgeon does not do the operating. His hands are still idle. This is true to a large extent, but he is seeing cases, is in contact with patients, with teaching, ward rounds, etc., and he can, if he so desires, take an occasional case, if the resident is getting an ample number.

This or some similar plan is suggested to help the applicants for certification. At the same time, it may aid in strengthening the ward services, surgical dispensaries, and may help in the development of future teachers.

—*Walter D. Wise, M.D.*
Baltimore, Md.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

RECENT ADVANCES IN SURGERY OF THE THYROID GLAND

HOWARD R. MAHORNER, M.D., NEW ORLEANS, LA.
(From the Department of Surgery, Tulane University School of Medicine)

THE HISTORICAL BACKGROUND

SURGERY of the thyroid, unlike certain other types of surgery, was comparatively well advanced toward its present position even at the turn of the century. Though much knowledge has very recently been added to our information concerning the thyroid gland, a student of the history of the subject must experience some misgivings on finding that with the exception of a few important improvements in the present century some surgeons in the last century achieved almost as much in the surgical management of goiter as is being accomplished today. In a résumé of the advances which have been made in recent years, it is by no means irrelevant to review in a cursory manner the important steps which brought the surgery of the thyroid to the commendable position it already occupied at the beginning of the century.

Desault[1] is accredited with being the first to successfully remove a goiter, an operation which he performed in 1792. At that time rarely were attempts made to operate for goiter. Its surgical extirpation was considered practically impossible. A few sporadic reports were made of such operations. One of the most remarkable early achievements was that of Hedenus,[2] who reported in 1821 that he had removed six goiters successfully and stated that he undertook the operations "to show my students what the operator who has courage, determination, composure, perseverance, and patience, and who is equipped with adequate anatomical and surgical knowledge can accomplish even in the severest cases with the bistoury for the good of mankind."

In the years prior to antiseptic surgery, not only hemorrhage but severe cervical cellulitis and mediastinitis were the barriers to the successful performance of this operation. In Billroth's[3] preantiseptic period, he did 20 operations on the thyroid gland. There were 8 deaths, 6 of which were due to infection. As late as 1883, Billroth[4] said: "If we were compelled to cut through the middle of the gland we would

Received for publication, June 25, 1937.

be confronted with quite an uncontrollable hemorrhage." Mikulicz[5] was one of the first to realize the advantages of removal of part of the tissue of each lobe, and found that he could control the hemorrhage even if he cut through the parenchyma of the gland. He devised an operation similar to the one we use today, a bilateral partial resection. In the period immediately following the introduction of antiseptic surgery, Billroth[6] operated upon 48 cases for goiter, with 4 deaths, 8.3 per cent mortality. To Theodore Kocher[7, 8] belongs great credit for perfecting the operation of thyroidectomy and for being the first to do a large number of cases. He used the collar incision,[8] the origin of which is usually ascribed to him, but it was previously recommended by Boeckel.[9] Gley,[10] in 1891, showed that the parathyroid glands were essential to life, and later Vassale and Generali,[11] in 1895, studied the function of the parathyroids and showed their relation to tetany. According to Dubois,[12] Frederic Müller was the first to show that the metabolic rate was increased in hyperthyroidism. Magnus-Levy,[13] in 1895, demonstrated an increase in oxygen consumption in Basedow's disease, and showed that it returned to normal after recovery from thyroidectomy.

Murray,[14] 1892, was the first to use thyroid extract in the treatment of myxedema.

In 1897, Theodore Kocher[8] reported 1,250 thyroidectomies, and in the last 175 cases had no deaths. Thus, at the beginning of the century, though little was known of the physiology of the thyroid gland, some men, notable among whom were Kocher[8] and Halsted,[15] were performing thyroidectomy with success in many cases and with an appreciably low mortality.

ETIOLOGY

The etiology of goiter, while still obscure, has been under close investigation by many authors, and the information gained, especially in recent years, is encouraging, so much so that some disclosures appear to be enticingly near the solution of the problem.

It has long been known and felt that iodine or a deficiency of it was in some way closely bound up with the cause of goiter. It has also been appreciated that throughout the world, especially in mountainous regions and glacial belts, goiter is prevalent. The geographical characteristics and location of goiter have been investigated in recent years by de Josselin de Jong,[16] Hellwig,[17, 18] Turton,[19] and Smith.[20, 21] Smith[20, 21] believes that the incidence of goiter is indirectly proportionate to the amount of solar radiation. Bircher[22] and others believe it is due to water supply. Bircher[22] found that when goiterogenic water was passed through a Berkefeld filter it rendered it free of the goiterogenic substance.

According to Hellwig,[18] the idea that excess calcium in the water is responsible for goiter is over a century old. As early as 1912,

Waller[23] advanced the theory that the essential factor in goiter seemed to be hard water supply. Hellwig's[18, 24] experimental evidence showed that rats fed on a diet deficient in iodine did not develop goiter, but if the diet was not only deficient in iodine but high in calcium chlorides goiter did develop. Hibbard[25] and Thompson[26] corroborate this evidence. Warthin[27] believes that in exophthalmic goiter patients have a typical constitution similar to that of status thymicolymphaticus.

Experimental and clinical evidence on the effect of the sympathetic nervous control of the thyroid gland as an etiologic factor in goiter is not convincing. Work has been done in this field by Cannon,[28] Wilson,[29] Marine, Rogoff and Stewart,[30] and Reid and Holman.[31]

Halsted[32, 33] concluded from microscopic studies on thyroid glands of dogs with low grade infections that infection caused hyperplastic changes in the thyroid gland. Cole and Womack[34, 35] found hyperplastic changes in the thyroid gland following infections in other parts of the body. Mahorner[36] performed similar experiments and found evidence to the contrary.

The possible relationship between psychogenic factors and diffuse toxic goiter have in recent years again been acknowledged by Plummer and Mayo,[37] Mittelmann,[38] and Geyer.[39]

Licini[40] after extirpation of the pancreas in dogs found an increase of colloid in the vesicles of the thyroid. On the theory that the thyroxin is a compound of tyrosine and iodine and that a deficiency of tyrosine might result from an absence of tryptic digestion due to poor pancreatic function, Davis, Hinton, and Killian,[41] and Hinton, Morton, and Weeks[42] ligated the pancreatic ducts in dogs and found a storage of colloid with an increased amount of iodine in the thyroid.

Marine and Baumann[43] by excision or injury to the adrenal gland of animals found an increase in metabolism, a condition analogous to exophthalmic goiter.[44, 45] Mahorner[36] failed to find histologic changes in the thyroid gland of dogs under similar experimental conditions. Other evidences of the relationship between the suprarenal and thyroid glands, though not entirely consistent, are the reports by Shapiro and Marine[46] and Tsuji[47] that improvements in patients with hyperthyroidism followed the administration of suprarenal gland; and the reports by Crile[48] that symptoms of hyperthyroidism abate after a denervation of the suprarenal gland, and the recent report of Pemberton[49] of an apparent mitigation of postoperative hyperthyroid crises from the administration of suprarenal cortex, sodium chloride, and sodium bicarbonate and sodium citrate.

Marine,[50] as early as 1914, showed that feeding brook trout hog liver and hog heart produced goiter in the fry in four months and concluded that some other factor than depletion of iodine was causative in the production of goiter. The possibility that some extraneous

goiterogenic substance may be responsible for the disease has been definitely demonstrated experimentally by Webster and others.[51-55] The question as to whether irradiation of the cabbage would change its goiterogenic quality was studied by Westra and Hunter.[56] McCarrison[57] found that soya bean and groundnut would produce goiter in rats provided there was a deficiency of vitamins in the diet. Other clinical and experimental work by McCarrison[58-61] has shown that the following factors are operative in the production of goiter: filth, ingestion of contaminated material, unsanitary conditions, vitamin deficiency, and an excess fat or calcium with a deficiency of vitamin A, B, or C.

Spence[62] found that injecting chickens intramuscularly with methyl cyanide, to which they are resistant, resulted in some goiterogenic action when large doses were used. Cole, Womack, and Ellett[63] studied 90 chemical compounds for goiterogenic properties and found that histamine, xanthine, caffeine, theophylline, and theobromine apparently produced in the thyroid definite desquamation, loss of colloid, and beginning hyperplasia. Marine and Rosen[64] likewise produced chronic progressive bilateral exophthalmos in immature rabbits maintained on a diet of alfalfa hay and oats by daily intramuscular injection of methyl cyanide.

In recent years, studies on the influence of hormones of the pituitary gland on the thyroid gland have indicated a most interesting and most promising field of investigation for the possible cause of hyperthyroidism, suggesting very strongly that the fundamental seat of disturbance in a case of toxic diffuse goiter is the anterior lobe of the pituitary gland.

As early as 1911, Simpson and Hunter[65] called attention to the fact that there is evidence of increase in the size of the pituitary in the thyroidectomized animal. Benedict and Homans,[66] in 1911, found a marked fall of total metabolism in the hypophysectomized dog. Almost everyone is familiar with the classical work of Gudernatsch[67] (1914), who described the changes in tadpoles resulting from feeding them thyroid gland. An early metamorphosis was induced. In 1916, Smith[68] and Allen[69] found that in the hypophysectomized tadpole there was atrophy of the thyroid gland and retardation of metamorphosis. In 1920, Allen[70] performed experiments upon tadpoles, extirpating the thyroid or the hypophysis. Absence of the thyroid gland, he found, fully prevented metamorphosis, but transplantation of the anterior pituitary to the hypophysectomized amphibian resulted in a marked acceleration of growth. Smith and Smith,[71] in 1922, found that intraperitoneal injections of fresh anterior lobe substance made changes in the thyroid in previously hypophysectomized tadpoles. The changes were in the nature of a return to normal from an atrophic picture of the thyroid. These investigations were the basis for further research along these lines and numerous investigators[72-124] have almost uni-

formly reported that extracts of the anterior lobe of the pituitary injected into lower animals result in the following changes: (1) increase in the size of the thyroid gland to as much as sixty times the normal weight, as reported by Shockaert;[72] (2) a decrease in the amount of colloid in the thyroid gland; (3) an increase in the size and number of epithelial elements of the thyroid resembling that seen in the histologic picture of exophthalmic goiter; (4) an increase in the basal metabolic rate; (5) a loss of weight in the experimental animal; (6) exophthalmos; (7) decrease in the iodine content of the thyroid gland; (8) increase in the iodine content of the blood; (9) diminished glycogen content of the liver; and (10) early metamorphosis of tadpoles which is absent if the thyroid has been removed. In other words, repeated subcutaneous or intraperitoneal injection of extract of anterior lobe of the pituitary body into lower animals apparently stimulates the thyroid gland to activity, and in the absence of this hormone there is atrophy of the thyroid gland. In its excess, a condition is produced in lower animals which comes closer to being the clinical and pathologic picture of exophthalmic goiter than has ever been produced by any other method. However, one must not conclude definitely that the thyrotropic hormone of the pituitary gland in excess is the cause of hyperthyroidism. The studies are suggestive that such may be an operative cause, but they do not entirely prove that it is *the* cause in toxic diffuse (exophthalmic) goiter. Repeated injections of anterior pituitary hormone are not accumulative and apparently after a short time the thyroid gland returns to its normal appearance. Collip and Anderson[73, 74] felt that an antihormone developed in the blood, and they obtained an extract from the serum of a horse injected with thyrotropic hormone which inhibited the action of thyrotropic hormone or by itself depressed the metabolic rate of normal animals. Thompson and coworkers[75] found that the thyrotropic principle in the human elevated the basal metabolic rate but produced no change in patients with marked myxedema.

IODINE IN ITS RELATION TO THE THYROID GLAND

Kendall,[125] in 1915, isolated the active principle of the thyroid gland containing approximately 60 per cent iodine. He named this principle thyroxin. Harington[126] accurately determined its formula. Harington[127] believes that thyroxin and diiodotyrosine account for all the iodine in the thyroid gland. He thinks that the natural active secretion contains both thyroxin and diiodotyrosine. Abelin[128] found that diiodotyrosine mitigated the effect of thyroxin. Delcourt-Bernard[129] substantiated these findings. However, Lerman and Salter[130] conclude that diiodotyrosine is calorigenically potent so long as it is part of the thyroglobulin molecule, but loses its activity when separated. The relationship of iodine and iodine content of the gland to

its histology has been studied by Marine and Lenhart,[131] Mosser,[132] Jordi,[133] Rienhoff,[134] Curtis,[135] and others. Plummer[136] introduced the routine use of iodine as a preparation for operation in the exophthalmic goiter patient in 1922, and by this measure the mortality was tremendously reduced.[137] Many studies[138-148] continued to be made on the clinical effects of the administration of iodine to the thyrotoxic patient. The summary of studies in recent years concerning this problem is that in the diffuse toxic goiter (exophthalmic goiter), there is a sharp improvement on the administration of iodine, and that eventually the gland becomes refractory to the administration of iodine and no further improvement occurs. Many authors, including such experimentalists and clinicians as Marine[45] and Means,[149] continue to reiterate the fact that the administration of iodine to the toxic goiter patient as a therapeutic measure other than for preoperative preparation is wrong and does not give the patient the best chance of recovery, which he would have with surgery following preliminary iodine medication.

The determination of iodine in the blood is a long and difficult chemical problem (Aitken[150] and Perkin[151]). It has been found by several investigators that the blood iodine in the thyrotoxic patient is appreciably increased as a general rule. Lahey[152] believes that the determination of the blood iodine has some value in indicating the risk in operation in thyrotoxic patients. It was found that in 70 per cent of patients having blood iodines which were elevated preoperatively, multiple stage operations were performed in 17.9 per cent, while of 30 per cent of patients having hyperthyroidism with normal blood iodine preoperatively, multiple stage procedures were performed in 45.8 per cent, therefore disclosing the possibility that low blood iodine with thyrotoxicosis is indication of a severe grade of hyperthyroidism and one in which multiple stage procedures must be considered as offering the patients the best chance of recovery. Watson[153] described an iodine tolerance test whereby the relative rate of disappearance from the blood stream of intravenously injected iodine may be expressed. The observation suggested that the iodine tolerance test may be a means of providing evidence of diagnostic importance in cases of doubtful thyroid disease.

TESTS

The determination of the basal metabolic rate has been the most reliable and most constantly used test for estimating the activity of the thyroid gland, and the degree of severity of the hyperthyroidism.[154-156] However, because the basal metabolic rate is not always a true index of the risk of operating upon a patient with hyperthyroidism, new methods of estimating the severity of the disease and the risk involved have been sought. One method is the determination of the iodine content of the blood, as mentioned above. Goetsch[157] noted some relationship between the sensitivity to adrenalin and the

severity of the disease. His test, however, and the Kottmann reaction[158] have not been accepted as reliable. Recently, however, Brazier introduced a new test.[159-161] Regarding the body as a dielectric and depending upon the fact that the dielectric loss angle is specific for any material, that is to say, the qualitative measure of this property is independent of the size and shape of the piece of material upon which the measurement is based, Brazier found with a special apparatus for measuring the dielectric loss angle that in thyrotoxicosis the dielectric loss angle or impedance angle was much greater than the standard deviation in the normal. The impedance angle was decreased in myxedema and it was increased by thyroxin, and not by other drugs which were tested. For apparently careful work on this subject, Brazier was awarded the annual award of the American Association for the Study of Goiter. Robertson and Wilson[162] and Horton and coworkers[163] failed to confirm or substantiate Brazier's work.

Clinical estimates together with the basal metabolic rate remain for the present at least the most accurate methods for determining the severity of the disease, the risk involved in an operation, and the condition of the patient. The relationship of cholesterol to the thyroid gland has been studied by Hurzthal and Hunt[164] and by McGee.[165] Although apparently there is some relationship between cholesterol metabolism and the thyroid gland, the findings are not consistent enough and have not been standardized to the extent that the determination of the cholesterol in the blood will estimate the status of thyroid activity. Hurzthal and Hunt[164] found that hyperthyroidism caused a marked drop in blood cholesterol, while hypothyroidism results in a marked increase in the blood cholesterol. McGee[165] failed to find the definite correlation between the metabolic rate and the blood cholesterol.

PHYSIOLOGY

Besides physiologic activity of the thyroid gland discussed in other sections of this paper, a general discussion of this subject has been contributed by Marine,[166] Boothby,[167] Richter,[168] and others. More recent expansions of our knowledge of the physiology of the thyroid gland have been contributed by Kosdoba,[169] who found that the thyroid hormone increased the absorbing function of the endothelial system and the resistance of the individual, and by Galli,[170] whose experimental work showed that thyroidectomized animals tolerate a tuberculous infection better than normal animals.

ANATOMY

Several investigations have been made on the lymphatic connections of the thyroid gland by Mahorner and others,[171] Chouke and his coworkers,[172] and Rienhoff.[173] Halsted,[174] because of the possibility that hypertrophy of the thymus accounted for some of the symptoms

in exophthalmic goiter, in two cases not only did a lobectomy but removed part of the thymus. His deductions were inconclusive. Briane and Funck-Brentano[175] have recently studied variations in the arteries to the thyroid gland, and careful studies on the recurrent laryngeal nerve have been made by Berlin and Lahey,[176] and Berlin.[177] Berlin found that only 65 per cent of nerves course through the tracheoesophageal sulcus. In the remaining instances, the nerves usually traverse the regional zone or penetrate the thyroid gland itself. Special studies of the effect the enlarged thyroid has upon the trachea have been made by Lahey[178] and Schindler.[179]

New and Childrey[180] have studied vocal cord paralysis. Unilateral paralysis results in fixation of the cord in the medium or cadaveric position. The average duration of symptoms is from ten and one-half months to seventeen months. Paralyzed cords in the cadaveric position usually change from this position to the median line within a few months with return of the voice. If the condition is bilateral, dyspnea develops as the voice improves. Hoover[181] offers something material for the treatment of bilateral adductor paralysis. In seventeen of his eighteen cases the paralysis was related to a thyroid condition and in fourteen it followed the thyroid operation. The only method of treatment which the author found of value was submucous resection of the cords and larynx.

PATHOLOGY

Numerous studies on the pathology of the thyroid gland in disease and under experimental conditions may be found in the literature. Among these may be mentioned Marine and Lenhart,[182] Wilson and Kendall,[183] Zechel,[184, 185] Rienhoff,[134] Rice,[186] Hellwig,[187] Markowitz,[188] Roussy and others,[189] Rabinovitch and others,[190] Hertzler,[191] and Keilty.[192] Apparently there is definite relationship between the histologic picture of the thyroid gland and its physiologic activity. In certain nodular goiters this relationship is often difficult to demonstrate. Most observers today consider hyperthyroidism as one continuous disease process and make no distinction except that of the degree of acuteness between the so-called toxic diffuse goiter (exophthalmic) and the toxic nodular goiter. Ever since Plummer[136] differentiated exophthalmic goiter and adenomatous goiter with hyperthyroidism, there has been some controversy as to this question, and it is only settled or rather evaded by adopting the classification which best expresses our present knowledge and which is accepted by the American Association for the Study of Goiter[194] and the Standard Classified Nomenclature of Disease,[195] dividing goiter into nontoxic diffuse, toxic diffuse, nontoxic nodular, and toxic nodular, thus ignoring an attempt toward detailed correlation between the microscopic findings and the activity of the gland.

Special studies on the thymus gland in patients with exophthalmic goiter have been made by Blackford and Freligh[196] and Margolis.[197] Hypertrophy of thymus occurred usually in patients under forty years of age with exophthalmic goiter. Its significance is not entirely understood, but attention has already been called to the fact that Warthin associated it with Graves's constitution.[27, 193] Special studies have been made on the hearts of patients dying with hyperthyroidism by McEachern and Rake.[198] Cardiac hypertrophy was not a constant finding, and it was impossible to ascribe the cardiac phenomena to structural changes in the muscles. These same investigators,[199] recently studying the problem on an experimental animal, found that the administration of thyroxin to animals produced no recognizable changes from the normal in the heart or the tissues studied pathologically. On the other hand, Parenti and Poloni[200] found in rabbits with thyrotoxicosis induced by the administration of thyroid extract an immediate reaction of the muscles to the injection, consisting of serous exudate with cloudy swelling of the fibers and loss of transverse structure of the fibers, or homogenous appearance of the muscles, and an increase in protoplasm, indicating a moderate degeneration of the contractile part of the muscle.

Meyer,[201] studying congenital cysts and fistulas of the neck, reemphasized that to cure thyroglossal duct cyst there must be complete removal of the cyst, a portion of the hyoid bone, and the tissues running from the center of the hyoid bone to the foramen caecum.

Inflammatory lesions of the thyroid gland have been discussed in recent years by Graham and McCullagh,[202] Nestmann,[203] Rankin and Graham,[204] Clute and Lahey,[205] and Boyden and others.[206] Inflammatory lesions have been divided clinically by Clute and Lahey[205] into simply thyroiditis, suppurative thyroiditis, and chronic thyroiditis. The last, being the most common, may be more difficult to diagnose before operation. Myxedema may supervene after the parenchyma has been destroyed in the inflammatory process. Entire removal of isthmus and suture of ribbon muscles to the remaining lobes to present reformation of scar over the trachea has been advocated by Lahey.[207] Rankin and Graham,[204] discussing tuberculosis of the thyroid gland, found that it occurred in approximately 0.1 per cent of over 20,000 surgical specimens of the thyroid. The diagnosis was made microscopically. Rienhoff in discussing this paper called attention to the fact that possibly the microscopic appearance of tuberculosis in the thyroid gland is not a true indication of the presence of this disease: that guinea pig inoculations of specimens showing this appearance in his experience failed to demonstrate the tuberculous bacilli.

LIVER

Only recently has the frequency and severity of the pathologic changes of the liver in hyperthyroidism been appreciated, and in only

the immediate past has the clinical significance of these lesions been disclosed. For a long time it has been recognized (Habershon,[208] Sutcliff,[209] Eder,[210] Kohn,[211] Kerr and Rusk,[212] Kerr,[213] Crotti,[214] and Hertzler[191]) that jaundice occasionally occurs with severe hyperthyroidism. Weller,[215] studying the hepatic lesions in groups of autopsies of 44 cases showing thyrotoxicosis, found chronic parenchymatous hepatitis in 50 per cent of the livers. Assmann[216] showed that there was damage to the liver in exophthalmic goiter, the anatomic changes being fatty metamorphosis and in long-standing cases cirrhosis. Lewis[217] in studying 12 livers of patients dying from thyrotoxicosis found one weighing only 960 gm. and attributed it to alcoholic cirrhosis. Beaver and Pemberton[218] in an important study on the pathology of the liver in cases of exophthalmic goiter found on studying 170 cases at necropsy that 23, or 21.5 per cent, showed jaundice. The changes in the liver were divided into acute and chronic, the former being fatty metamorphosis and central and focal necrosis, and the chronic lesions being simple and subacute yellow atrophy or cirrhosis. Acute lesions were present in 91.5 per cent of the cases, and the liver weighed less than the normal in 62.5 per cent. Extremes in weight were 644 gm. and 2,450 gm. They found relationship between the degree of duration of thyrotoxicosis and the severity of liver damage. Mahorner[219] has shown that jaundice in hyperthyroidism due to toxic degeneration disappeared rapidly after the relief of the hyperthyroidism by resection of the thyroid.

The clinical importance of damage to the liver from hyperthyroidism has only slowly been appreciated by clinicians and surgeons. Youmans and Warfield[220] found clinical impairment in 50 per cent of livers tested for liver function by liver function tests. Kuriyama[221] found that the glycogen diminished in the liver in animals fed with thyroid extract. Eitel and Loeser[100] and others found that repeated injection of extract of the anterior lobe of the pituitary resulted in reduction of the glycogen content of the liver, apparently due to the fact that the thyroid was stimulated to a certain degree of hyperactivity. Lahey[152] advanced evidence to show that the severity of hyperthyroidism is in some measure proportionate to hepatic damage and insufficiency. Maes, Boyce, and McFetridge[222] substantiate this and believe the test to be a guide to clinical improvement before operation. Thus, only slowly has been appreciated the significant fact that the liver is damaged in hyperthyroidism, and its present-day practical status, the realization of the necessity for administration of dextrose as in other conditions in which there is liver damage. Probably a number of patients with severe postoperative reaction will not only be greatly benefited, but may be actually saved by the administration of larger quantities of dextrose intravenously.

MALIGNANT TUMORS OF THE THYROID GLAND

A number of worthy contributions have been made recently to the study of malignancy of the thyroid gland. In reviewing the literature, one is impressed with the total lack of uniformity in terminology and classification of the different types of tumors. The incidence of malignancy of the thyroid gland has been estimated by Graham[223] to be slightly less than 2 per cent of thyroids examined in the laboratory; by Clute and Warren[224] as 2.8 per cent of operated thyroids; by Pemberton[225] as 1.66 per cent of all benign enlargements of the thyroid coming to operation, and by Dinsmore and Crile[226] as present in 1 per cent of all patients subjected to thyroidectomy. This surprisingly high incidence of malignancy of the thyroid in those patients operated upon is justification for urging patients with nodular thyroids to have them removed. Pemberton[225] estimates that in 87 per cent of all cases there was evidence of preexisting benign goiter. Smith, Pool, and Olcott[227] found a preexisting adenoma in 92.6 per cent of the cases of thyroid malignancy. The metastatic lesions of tumors of the thyroid have been studied by Breitner,[228] Sutherland and others,[229] and Copeland.[230] Engelstadt[231] demonstrated that the metastases of carcinoma of the thyroid produced the active secretion of the thyroid gland, thyroxin. Pack and Craver[232] attempted to show by roentgenograms changes in the larynx resulting from thyroid tumors. This method is not to be relied upon for diagnostic accuracy. Mulvihill[233] compared the incidence of malignancy in Berlin with that in New York and believes that the American surgeons operate upon their cases early because they appreciate the indications for operation earlier in this country.

The proper treatment for carcinoma of the thyroid gland is surgery combined with x-ray or radium therapy (Graham,[223] Clute and Warren,[224] Pemberton,[225] Dinsmore,[226] Schreiner and Murphy,[234] Stewart,[235] de Quervain,[236] Dunhill,[237] Clute and Warren,[238] and Bowing[239]). Zuppinger and Rohrer[240] advocate fractional irradiation alone. The prognosis for cancer of the thyroid is not bad if extirpation can be accomplished followed by radiation therapy. Pemberton[225] reported that of 204 cases 32 per cent are living after a lapse of from three to eighteen years, and de Quervain[236] reported 54 per cent living after three years. Crile and Crile[241] in a recent article described a radical operation for malignant tumors of the thyroid gland. They emphasize that approximately 80 per cent of malignant tumors of the thyroid gland are malignant adenomas, and that malignant adenoma and papillary carcinoma are the only types of malignant tumors in their experience which have been cured by surgery. Since these tumors have a tendency to metastasize through the blood vessels, the veins, they describe an operation for excision of the entire lobe of the thyroid with the veins, even the internal jugular, on that side.

Aberrant thyroid glands have a tendency to become malignant. This subject has been discussed by Cattell[242] and Lazarus and Rosenthal.[243] Misplaced thyroid glands apparently develop from the branchial pouches. According to Lazarus and Rosenthal,[243] 70 per cent of the aberrant thyroids give rise to neoplasms of the papillary type. Complete excision results in a favorable prognosis. All cases should receive x-ray therapy postoperatively. Valdoni[244] described a case of malignancy of the thyroid gland in which metastatic lesions were found to extend into the jugular vein and fill it with an adherent tumor. The entire jugular vein together with its tributaries was resected and the patient was examined twenty months after operation with no evidence of recurrence.

CLINICAL ASPECTS

Attention has already been called to the controversy which still continues as to whether hyperthyroidism itself may be divided into one or several different types. Hertzler[245] considers all goiters as one disease process, the degree of toxicity being only a stage in the process. This concept is supported by Wendel.[246] Bram,[247] on the other hand, attempts to show the clinical points of difference, differentiating as two distinct entities toxic adenoma and exophthalmic goiter, as did Plummer previously. Fortune[248] again calls attention in recent years to the constitutional evidence of a distinct type that develops Graves's disease and pathologic evidence of Graves's constitution (Warthin[27]) in 90 per cent of the cases. Roeder and Killins[249] call attention to a type of hyperthyroidism in which there is a normal or subnormal basal metabolic rate with progressive exophthalmos, but with hyperplasia and hypertrophy of the cells of the follicles. Excellent descriptions of the clinical aspects of the disease may be found in many systems and monographs mentioned herein, and recently in a brief but noteworthy contribution by Pemberton and Haines[250] in Christopher's *Textbook of Surgery*. Mahorner[251] discussed the clinical aspects of goiter and called attention again to the characteristic nail changes in toxic goiter, illustrating them with photographs. Hill[252] studied hyperthyroidism with relation to the sex events in the female and found that the onset of toxicity was frequently coincident with one of the major changes, such as puberty, puerperium, or climacteric. Meldolesi[253] found menstrual disturbances in 76 per cent of cases of toxic diffuse (exophthalmic) goiter, which he termed "Flajani-Basedow's disease."* Amenorrhea was more frequent in the severe type of the disease. Studies by Mussey, Plummer, and Boothby[254] and Bothe[255] on the association of hyperthyroidism and pregnancy indicate that there is little doubt that the best prognosis for the mother and child is for the treatment to be directed to the thyroid,

*Parry described exophthalmic goiter in 1786, Flajani in 1800, Graves in 1835, and Basedow in 1840.

the treatment, especially in the severe type of the disease, being extirpation of the gland. The prognosis is good when this is done. Helmholz,[256] McGraw,[257] and Cattell[258] have made contributions on the study of thyroid disorders in childhood. According to Cattell,[258] approximately 1 per cent of patients with thyroid disorders are under thirteen years of age. Hyperthyroidism is generally more severe in children, and it should be treated by the same measures as it is in adults. Duncan[259] has called attention to the fact that both hypothyroid and hyperthyroid states, despite their contrast in clinical picture, are associated with arthritic syndromes. In hyperthyroidism the capsular and periarticular changes, usually in the upper extremity, are similar to those in atrophic polyarthritis. The condition is corrected by surgical resection of the thyroid gland.

Recently attention has been called to the association of exophthalmic goiter with several diseases of the central nervous system. Cohen and King[260] noticed simultaneous occurrence of myasthenia gravis and exophthalmic goiter. Mussio-Fournier[261] reports five cases of familial infantilism due chiefly to hypophyseal insufficiency, but with an associated thyroid insufficiency. The subjects were a brother and four sisters. Thyroid insufficiency was probably secondary to hypopituitarism. Dunlap and Kepler[262] recorded the unusual relationship of exophthalmic goiter with the peculiar syndrome of familial periodic paralysis, in which true paralysis occurs sporadically. In four cases in which they found the association, none of the attacks of paralysis occurred prior to the development of the symptoms of exophthalmic goiter. The plausible explanation appeared that recurrence of attacks of paralysis was an inherited characteristic and the exophthalmic goiter was the precipitating factor. The possibility of goiter's being an hereditary dominant characteristic was present in a family reported by Bing.[263]

A possible relationship between the activity of the thyroid gland and the reticuloendothelial system has been noted above. Pascual and coworkers[264] placed emphasis on the relationship between the thyroid and hemoglobin metabolism, which they say is manifested by the anemia which accompanies myxedema, by the fact that hyperthyroidism may be associated with hyperbilirubinemia, and by the fact that splenomegaly is frequently noted in hyperthyroidism. They noted that the administration of splenic extract in patients with hyperthyroidism resulted in a fall in the basal metabolic rate. Treatment of hyperthyroidism, they declared, decreases the hemoglobin metabolism and lowers the blood pressure. Another conjecture about a relationship between the thyroid gland and the blood is cited by Friedgood[265] who, because lymphatic leucemia is usually associated with an elevation of the basal metabolic rate and because of the depressing effect of iodine on basal metabolism in exophthalmic goiter,

studied the effect of Lugol's solution on the metabolic rate, clinical picture, and laboratory findings in cases of lymphatic leucemia. The administration of Lugol's solution produced a response similar to that seen in exophthalmic goiter. From this the author concludes that exophthalmic goiter is not a disease of the thyroid gland, but primarily a disturbance of the sympathetic nervous system. In some cases of lymphatic leucemia Lugol's solution seems to increase the hemorrhagic tendency and to lower the erythrocyte count and the hemoglobin. There was reduction of nervous manifestations and the size of the lymph nodes and the total leucocyte count. Hubble[266] in reviewing the literature on the influence of the endocrine system in blood disorders found the general impression to be that the thyroid hormone stimulates the formation of erythrocytes and lymphocytes and thus has a tendency to depress granulocytes.

From a clinical study, Golden and Abbott[267] concluded that hyperthyroidism produced an abnormal elimination of calcium. Cohen,[268] because of the association in the same individual of leg ulcers and myxedema and the prompt response of both to thyroid extract, believes that there is a relationship between circumscribed myxedema of the legs and leg ulcers in which there is an obscure etiology.

Certain advances in the knowledge of the relationship between the activity of the thyroid gland and carbohydrate metabolism have been made in recent years. Attention has already been called to the disappearance of glycogen from the liver in the hyperthyroid state. Hatlehol[269] investigated carbohydrate tolerance in hypothyroid and hyperthyroid states and found pronounced disturbances in the hyperthyroid state which were corrected by thyroidectomy. John[270] in an excellent paper on hyperthyroidism and carbohydrate disturbances found that the average incidence of true diabetes in hyperthyroid patients was 2.3 per cent; whereas, the incidence of hyperthyroidism in diabetic patients is 1.68 per cent. After operation for hyperthyroidism, diabetics improved in 55 per cent of the cases, remained stationary in 15, became worse in 30. Recently, Wilder, Foster, and Pemberton[271] found slight improvement following total thyroidectomy for diabetes, but not enough to justify adopting the procedure for routine treatment for severe diabetes. Womack and Cole[272] record two cases showing clinical and pathologic evidence that the thyroid gland tends to undergo compensatory hypertrophy when there is hypoglycemia due to hyperactivity of the islands of Langerhans. Hyperthyroidism masked under the appearance of gastrointestinal symptoms, hypertension, and cardiac disease has been the subject of papers by Verbrycke,[273] Parkinson and Hoyle,[274] and Towers.[275] It has long been known that the predominant symptoms of hyperthyroidism may be cardiac. Only the failure to think of the possibility of the thyroid's being the fundamental cause of a heart condition should ever result in an incomplete diag-

nosis. Excellent discussions of the cardiac features of goiter have been made by Pemberton and Willius[276] and Lahey,[277] both striking a note of hopefulness for this seemingly seriously ill group of patients. Even in the face of complete cardiac decompensation, the result of hyperthyroidism, thyroidectomy will result in a dramatic cure.

To Lahey[278] goes the credit of identifying a type of clinical picture of hyperthyroidism in which the prognosis is extremely grave, though to all appearances the patient may be a safe risk. He calls it apathetic thyroidism. The clinical picture is characterized by an appearance of nonactivity, apathy, hyperthyroidism with relative inactivity. The pulse varies from 100 to 120, and the basal metabolic rate from 20 to 40 with a relatively small thyroid. Lahey[278] warns against too early and too much surgery in these individuals in whom the disease is much more severe than it appears.

Thyroid tissue tumors of the ovary have been discussed recently by Masson and Mueller[279] and Sanders.[280] No less than 80 cases of struma ovarii were found in the literature by Sanders,[280] who reported a large ovarian thyroid tumor.

An excellent review of the subject of lingual thyroid has recently been made by Montgomery.[281] By lingual thyroid the author refers to thyroid tissue occurring at the base of the tongue, rarely in the body of the tongue. There are approximately 144 authentic cases on record. The symptoms are dysphagia and dysphonia, rarely hyperthyroidism. In 75 per cent of the cases the thyroid is absent in the neck. Postoperative hypothyroidism occurred in 70 per cent of cases in which the lingual thyroid was removed. Because of this fact, the author recommends trial medication of desiccated thyroid and iodine, if biopsy discloses no urgent indication for excision.

Oswald[282] and others have called attention to the simultaneous occurrence of myxedema and hyperthyroidism. This paradoxical condition is apparently not rare in postoperative states and is essentially the coexistence of certain features of each condition.

EXOPHTHALMOS

Recent investigations have given a more acceptable explanation of the true nature of exophthalmos in toxic diffuse goiter. As early as 1910, Gley[283] reported the spontaneous development of exophthalmos in thyroidectomized animals. Shockaert[72] was able to produce exophthalmos in ducks by the repeated injections of anterior pituitary hormone. Loeb and Friedman[105] and Friedgood[284] produced exophthalmos in guinea pigs by repeated injection of anterior pituitary hormone. Friedgood[284] confirmed this observation and believed that the ability of the anterior pituitary extract to induce prominence of the eyes is more apparent in the presence of hypothyroidism than in hyperthyroidism. This may in some measure explain certain increases clini-

cally in the degree of exophthalmos after thyroidectomy. Marine and Rosen[285, 64] produced exophthalmos in immature animals by injecting pituitary extract and by injecting cyanide, preferably methyl cyanide, into animals kept on a diet of alfalfa hay and oats. The removal of superior cervical ganglion completely abolished exophthalmos produced in rabbits by cyanide administration, at least during the first two or three months of its existence. Several papers concerning ephedrine and adrenalin in hyperthyroid states have substantiated the experimental observations of Marine and Rosen[285] concerning the sympathetics. Justin-Besançon and coworkers[286] found that of a number of drugs tested, ephedrine was the most likely to produce exophthalmos. Thyroxin alone did not produce the symptoms, but sensitized the animal to the effect of ephedrine and adrenalin and other sympathetic stimulants. Labbe and coworkers[287] found that when thyroxin was given in daily doses of 10 mg. to obese persons, signs of hyperthyroidism developed but no exophthalmos. When, however, 50 mg. of ephedrine were injected ten minutes after the administration of thyroxin, marked exophthalmos resulted within five minutes and persisted for two hours. These observations are further substantiated by Sainton and Hesse,[288] who observed in an obese patient with a low metabolic rate that administration of thyroxin rapidly reduced her weight and raised her metabolism. Finally the patient was placed on thyroxin and 15 drops of adrenalin by mouth. The basal metabolic rate rose to +59 and marked bilateral exophthalmos developed. When the adrenalin was discontinued the exophthalmos disappeared in four days. These striking findings would seem to indicate that exophthalmos is due to sensitization of the sympathetic system to adrenalin by thyroxin. Clinical studies of exophthalmos in recent years have been made by Reudemann,[289] Cattell,[290] and Plummer and Wilder.[291] Plummer and Wilder found that the incidence of association of exophthalmos with diffuse toxic goiter is now only about 40 per cent, as it has decreased in recent years. Plummer and Wilder[291] explain the occurrence of exophthalmos in toxic goiter by spastic contraction of fibers of Müller's muscles which act against weakened extraocular muscles. Indications available indicate that there is little edema and very little venous congestion and that the orbital muscles are small and degenerated. Cattell[290] found that exophthalmos is present in 46 per cent of 860 cases of exophthalmic goiter. Exophthalmos was completely relieved in 50 per cent of the cases operated upon, improved in an additional 13 per cent, not improved in 22 per cent, and in 1 per cent it increased after operation. Zimmerman[292] has considered the group of patients developing exophthalmos after operation.

King[293] postulates that exophthalmos develops because of the accelerated circulation in the orbital cavity, more blood entering than

can be readily evacuated by the vein, resulting in edema and connective tissue formation. Naffziger[294] has devised and successfully used an operation for malignant progressive exophthalmos. Naffziger's operation consists in removing the roof of the orbit for decompression. He found the extraocular muscles greatly increased in size, which increase histologic examination showed to be due to the presence of edema, round cell infiltration, and fibrosis, rather than to a true hypertrophy of the muscles.

POSTOPERATIVE PARATHYROID TETANY

After clinical studies on postoperative tetany, Sjostrom[295] called attention to the fact that the condition tends to become latent. Though the patient may be fully capable of working, calcium content of the blood may remain low. The relationship between the thyroid and parathyroid glands has been discussed by Ask-Upmark,[296] who calls attention to the relation of the thyroid to the mineral metabolism as evidenced by the fact that calcium intake as well as iodine deprivation favors the development of goiter. The thyroid exerts an influence upon calcium and phosphorus metabolism. An excellent discussion of tetany with detailed methods of management has been presented by Boothby, Haines, and Pemberton.[297] Calcium and viosterol suffice for the milder forms. Parathormone may be used in the more severe cases. A very significant piece of work has been presented by Stone, Owings, and Gey,[298] who point out the possibilities of transplantations of living grafts of thyroid and parathyroid glands. In order to adapt the graft to the host, they first culture the tissue to be transplanted in an artificial tissue medium containing the body fluids of the recipient. Grafts thus transferred are more likely to survive. In two cases in human beings they were able to relieve the symptoms of parathyroid deficiency by transplanting tissue in this manner. An equally significant presentation is that of Levine,[299] who following an original attempt by Oppel, in 1925, to cure parathyroid tetany by transplantation of a segment of bone so treated a patient who had active postoperative tetany. Convulsions disappeared shortly after the bone transplantation and even before blood calcium was increased. Convulsions had responded only temporarily to injections of calcium, but after implantation of a fragment of bone 6 cm. long, 2 to 3 cm. wide, and from 8 to 10 cm. thick, recovery ensued.

TOTAL THYROIDECTOMY

The commendable work of Blumgart and his coworkers[300-304] on the velocity of blood flow was a factor which led to a new treatment for intractable heart disease in individuals with a normal thyroid gland. The work of Blumgart and his associates principally showed that the rate of blood flow was proportionate to the basal metabolic rate. In hyperthyroidism it was increased, in myxedema it was decreased.

Also, in chronic heart disease with decompensation it was decreased. An additional observation made by Levine,[305] that improvement followed subtotal thyroidectomy in a patient suspected of having masked hyperthyroidism but in whom histologic examination proved the gland to be normal, suggested that the extirpation of the normal thyroid might be helpful in cardiac failure not due to thyrotoxicosis. Other studies by Rosenblum and Levine[306] on patients with hyperthyroidism and heart disease led them to conclude that the occurrence of striking improvement following subtotal thyroidectomy in a patient with advanced congestive heart failure in whom the thyroid was normal suggested that this operation on the normal thyroid might be of value in treatment of various forms of cardiac disease. The first cases[306] in which thyroidectomy was deliberately undertaken in patients with congestive heart failure in whom the thyroid gland was clinically normal had only a subtotal thyroidectomy and only a temporary improvement. Surgeons were urged to take out more and more of the gland and eventually total thyroidectomy was done in all instances in which it was desirable to reduce the basal metabolic rate and thereby the velocity of the blood flow to a level commensurate with the abilities of the heart. Numerous other articles[307-322] have been written on the subject, mostly by Blumgart, Levine, Berlin, Cutler, and Eppinger. In a summary of the work by Berlin,[317] he states that approximately 70 per cent of the patients with either angina pectoris or congestive heart failure who were operated upon from one to two and one-half years ago have shown marked to moderate improvement. There was an absence of mortality in the last 62 cases admitted for operation. Most observers agree now that poor results are due to difficulty in selecting cases. Clark, Means, and Sprague[318] outline the following contraindications: (1) cases in which the patient has not been given the benefit of entirely adequate medical treatment over a sufficient period of time to evaluate medical care; (2) cases showing rapid progressive cardiac condition in spite of medical care; (3) cases in which the heart disease is so severe that the patient is unable to establish and maintain compensation on treatment with digitalis and bed rest; (4) cases with high grade mitral stenosis or other mechanical defects giving rise to high venous pressure which is sustained after the restoration of compensation; (5) cases with low preoperative metabolic rate (Berlin and Blumgart[312] state that a B.M.R. of –20 per cent or below is contraindication); (6) cases with severe renal insufficiency; (7) cases with chronic pulmonary disease of any type; (8) cases with malignant or severe hypertension, especially if this is associated with generalized arteriosclerosis; (9) cases with active rheumatic infection, bacterial endocarditis, etc.; (10) cases with recent coronary thrombosis; and (11) cases with status anginosus. There remain certain cases of intractable incapacitating heart disease in which total thyroidectomy is not contraindi-

cated and in which it may be beneficial. Parsons and Purks,[320] collecting information from various sources, summarize the results in a manner that would indicate that the operative mortality from congestive heart failure is approximately 10 per cent, that the results are excellent in approximately 35 per cent of cases, and that satisfactory improvement is attained in approximately 60 per cent. For angina pectoris, the results were even better. Excellent results were obtained in 55.5 per cent and moderate improvement occurred in 28.12 per cent. They believe that the status at present is that good or satisfactory improvement occurs from total thyroidectomy in angina pectoris in 80 to 90 per cent of the cases.

It is desirable to keep the basal metabolic rate in these cases postoperatively at approximately –20 to –30.[314] The troublesome symptoms of myxedema do not become apparent as a general rule until the basal metabolic rate reaches –30. Small amounts of thyroid extract in those cases with definite myxedema (grain 0.1 to 0.5 daily) are sufficient for relieving the distressing symptoms and still keeping the metabolism at levels of approximately –25 to –30. Hertzler[321] looks askance at the subject. He says: "If this is kept in mind, one is forced to recognize the possibility that pronounced cardiac improvement is presumptive evidence that the thyroid gland was diseased and that the removal of it acted not so much as removing the whip as in removing toxic products which were injuring the heart."

The present status of the subject seems to be that there are certain cases of intractable heart disease that are definitely benefited by a total thyroidectomy so that these unfortunate individuals may return to work after such surgery. Likewise, the patient with angina pectoris in the medium between status anginosus and occasional sporadic attacks of pain may expect enough benefit from the operation to justify its being done. Let it be recorded here that Blumgart and Davis[314] report that massive doses of roentgen irradiation applied to the normal thyroid are ineffective in producing a persistent lowering of the basal metabolic rate.

MYXEDEMA

Some advances in our knowledge, especially of the therapy of myxedema, have been made recently, due in large part to the deliberate production of total thyroid deficiency for the treatment of heart disease. Thompson and his coworkers[323] attempt to show that thyroid extract from different animals gives the same result in myxedema if the iodine content is the same. Means[149] and Lerman[324] have given splendid discussions of the therapy in myxedema. Complete myxedema they regard as a metabolism –30 per cent below normal, or lower. They have studied the question of dosage of thyroid and find that in the completely myxedematous patient one-half grain of thyroid extract daily will maintain the basal metabolic rate of most cases about –20 per cent below zero. One grain maintains the rate at about –10 per cent,

one and one-half grains at about –5 per cent, and three grains at about zero or standard level. They do not believe it is necessary to raise the metabolic rate to zero. In their experience patients rarely have symptoms of myxedema when the basal metabolic rate is above –20. Blumgart and Davis[314] have found that amounts of thyroid extract varying between one-tenth and one-half grain daily are sufficient to relieve the individuals from distressing symptoms and still permit the metabolism to remain low. De Wesselow[325] advocates a small dose, one-half grain, of desiccated thyroid daily, increasing until a full maintenance dose of two or three grains daily is reached. Kena-Apajalahti,[326] studying the question of infantile myxedema, reiterates the already appreciated fact that the effect of thyroid therapy is not equally favorable in all cases.

THERAPY FOR HYPERTHYROIDISM AND FOR GOITER

Surgery occupies in the clinics as well as in the literature the place of supremacy in the treatment of goiter, toxic or nontoxic. Though so far it has not made a significant impression, there is continually a repetition of attempts to cure goiter by other means. Such attempts fall in two categories: first and more commonly, into that of radiation therapy advocated by roentgenologists and radiotherapeutists; second, into a smaller and possibly even more commendable group of investigators attempting to supplant surgery and destructive means by some form of therapy that would correct the derangement that is responsible for the changes in the thyroid gland. All authors agree that x-ray or radium therapy in conjunction with surgery is the proper therapy for malignancy of the thyroid gland. For the treatment of toxic goiter or other types of goiter by irradiation therapy an appraisal of the value of the method may be obtained from the following quotations: Soiland, Costolow, and Meland[327] of 3,100 cases treated by irradiation therapy report 73 per cent clinically well, 16 per cent improved, 11 per cent unimproved. Goodwin and Smith[328] state that their objection to x-ray is that too much time is consumed. Hayer,[329] reporting on the treatment of 107 patients with thyrotoxicosis by x-ray, found 70.5 per cent improved, 9 per cent worse, 1.3 per cent dead. Engel[330] reports the rather uncommendable figures of a mortality of 13.6 per cent of surgically treated patients and 14.3 per cent for radiologically treated cases of Basedow's disease. Quigley[331] reported favorable results in approximately 70 per cent of patients with toxic goiters treated by radium therapy. In cases of toxic adenoma subsequent operation was required in approximately 50 per cent. Parcelier[332] states that when x-ray irradiation is beneficial the improvement occurs slowly so that at least six months must be allowed for the treatment. In at least 30 per cent of the cases no improvement occurred. Williams,[333] reporting on the x-ray treatment of goiter, stated that in his 200 cases an average of 10 treatments

were given in three and one-half months. Eighty and one-half per cent of the patients were definitely cured and 13.5 per cent were benefited. Menville[334] in a collected series totaling 10,541 patients found that radiation was followed by cure in 66.2 per cent of cases, marked improvement in 21 per cent, and recurrence in 8.45 per cent. Lüdin,[335] who states that the results of irradiation treatment in Basedow's disease are disputed chiefly by surgeons and that the chief disadvantage of irradiation is the greater frequency of recurrence, says that death following irradiation treatment in cases of patients considered too poor risks for operation occurs in spite of rather than because of irradiation. Dunhill[336] says that 140 of his patients who have had x-ray irradiation under favorable conditions came to operation eventually. Gallino[337] says that irradiation therapy for hyperthyroidism is contraindicated in subacute cases, cases with grave cardiac disease due to thyrotoxicosis, hyperthyroidism accompanied by marked pluriglandular disturbances, and forms of hyperthyroidism with nodular tumoral forms of enlargement of the thyroid gland, especially those with pressure symptoms. Other advocates of irradiation therapy for goiter are Allison,[338] Gerber,[339] Schteingart,[340] and Zweifel.[341] Gerber[339] says that it is not advisable to treat patients with high basal metabolic rates, patients with extremely large glands, and cases in which there are cardiac changes. Apparently in such a controversy existing between a minority of roentgenologists and a majority of surgeons the clinicians will be the unbiased observers. Suffice it to say that two outstanding investigators in that field, Marine[45] and Means,[149] believe that at present the best therapeutic program available for hyperthyroidism is subtotal thyroidectomy in the fully iodinized subject.

Attention has already been directed to attempts to establish some delicate test for indicating prognosis and for determining the operability of patients with toxic goiter. Seed[343] recently reemphasized certain clinical standards, especially that stationary or increasing weight indicates that the condition is improving and offers a good prognosis, that muscular strength is also a valuable index, and that a patient who is able to step up on a chair without assistance is able to withstand the operation.

Attention has already been called to attempts to relieve hyperthyroid crises by suprarenal extract (Pemberton[49]) and sodium chloride. Starr and Patton[343] have treated 13 cases of hyperthyroidism with extracts of pregnancy urine or theelin. It appears that the induction of a remission by extract of pregnancy urine is dependent upon normal ovarian functions. Remission occurred in 7 of the cases. In 6 cases the treatment failed entirely. Pemberton[344] and Jackson[345] have studied the problem of persistent and recurrent hyperthyroidism. Jackson[345] suggests for the prevention of both the elimination of focal

infection, strain, and occupational factors, permanent abstinence from coffee and other stimulants, and the long-continued use of iodine postoperatively.

The mortality for operation for goiter and the end-results of thyroidectomy for toxic and nontoxic goiter have been reported by many authors. A general résumé of the subject has been given in a splendid article by Boothby.[137] In general, the mortality by a number of surgeons is less than 1 per cent. Thompson, Taylor, and Meyer,[347] in a study between the preoperative condition of the patient and the operative mortality, say the operative mortality is partly due to the skill of the surgeon. This is obviously true, and to demonstrate that all the laurels do not belong to those centers dealing with large numbers of goiters, commendable are the reports of Horsley (Richmond),[348] who had no mortality in 183 consecutive thyroidectomies, and Drennen (Birmingham),[349] in whose series there was 1 death in 300 consecutive thyroidectomies. Goetsch,[350] studying the cause of mortality after thyroidectomy, found that approximately one-third of the patients died of hyperthyroidism. Maes and his coworkers[222, 351] have studied the problem of goiter in the negro and in the nonendemic area. Other studies on mortality and therapeutic failures have recently been made by Rogers[352] and Elkin.[353] Noehren[354] finds that the incidence of cure three months after operation is between 80 and 90 per cent following thyroidectomy. Coller and Potter[355] found rehabilitation in over 90 per cent of patients operated upon for exophthalmic goiter, 95 per cent respectively for cases with toxic adenoma and nontoxic goiter. Richter[346] reports successful results in thyrotoxicosis from operation in 98.4 per cent of cases. Unfortunately, certain reports, notably those of the foreign clinics (Engel,[330] Wallace and Wevill[356]), have high mortality rates from thyroidectomy.[137]

SPECIAL TECHNIQUES

The operation for thyroidectomy can be found described in numerous monographs and chapters and sections quoted and unquoted herein. Attention is called here to only a few unusual aspects of thyroidectomy. The operation for total thyroidectomy is adequately described by Berlin.[309] Emphasis is placed upon direct observation of the vocal cords for possible injury having occurred to the recurrent laryngeal nerve after the first lobectomy. Descriptions of operative technique for substernal and intrathoracic goiters have been given by Pemberton,[357] Lahey,[358] Clairmont.[359] Splitting the sternum is rarely necessary. The operations of Crile[241] for malignancy and of Lahey[207] for thyroiditis have been mentioned. Questionable are the procedures even recently advocated by Waterworth,[360] aspiration of cystic nodules with injection of a few drops of iodine, and Shaw,[361] cervical sympathectomy where symptoms are of such degree of severity as would contraindicate lobectomy of the thyroid.

RECENT REVIEWS AND RÉSUMÉS

A number of commendable reviews have been made concerning the thyroid literature and the various phases of the thyroid problem within the last few years. Among many deserving special commendation are those of Marine,[362-364] Zimmerman,[365] Starr,[366] Boothby,[137] Means.[149] Of recent texts deserving attention there should be included Rienhoff,[134] Hertzler,[191] George Crile and his associates,[367] Eberts, Fitzgerald, and Silver,[368] Crotti,[214] Sloan,[369] and Means.[370]

REFERENCES

1. Bichât, X.: Oeuvres chirurgicales de Desault, Troisienne Edition, Paris **2**: 298, 1813.
2. Hedenus, J. A. W.: Ausrothung der Schildruse, J. de Chir. und Augenheilk. **2**: 237, 1821.
3. Billroth, T.: Chirurgische Enfalrungen, Chirurgische Klinik Zurich, 167, Berlin, 1869, A. Hirschwald.
4. Idem: Discussion of paper by Weiss, N.: Zur Pathologie und pathologischen Anatomie der Tetanie, Wien. med. Wchnschr. **33**: 683, 1883.
5. Mikulicz, J.: Beitrag zur Operation des Kropfes, Wien. med. Wchnschr. **36**: 1, 70, 96, 1886.
6. Billroth, T.: Quoted by Halsted, Ref. No. 15.
7. Kocher, T.: Ueber Kropfextirpation und ihre Folgen, Arch. f. klin. Chir. **29**: 254, 1883.
8. Idem: Chirurgische Operationslehre, Jena, 1897, Gustav Fischer.
9. Boeckel, J.: Thyroidectomie pour un goître suffocant; guérison por première intention, Mem. Soc. de méd. de Strasb. **17**: 129, 1881.
10. Gley, E.: Sur les fonctions du corpo thyroide, Compt. rend. Soc. de Biol. **3**: 841, 1891.
11. Vassale, G., and Generali, F.: On the Effects of Extirpation of the Parathyroid Glands, Alienist & Neurol. **18**: 57, 1897.
12. Dubois, E. F.: The Respiration Calorimeter in Clinical Medicine, Am. J. Med. Sc. **151**: 781, 1916.
13. Magnus-Levy, Adolf: Ueber den respiratorischen Geswichsel unter dem Einfluss der Thyreoiden Sowie unter vesschieslenen pathologische Zustänaden, Berl. klin. Wchnschr. **32**: 650, 1895.
14. Murray, G. R.: Remarks on the Treatment of Myxedema With Thyroid Juice, With Notes on 4 Cases, Brit. M. J. **2**: 449, 1892.
15. Halsted, W. S.: The Operative Story of Goiter: The Author's Operation, Johns Hopkins Hosp. Rep. **19**: 71, 1920.
16. De Jong, R. de Josselin: Ueber Kropf in den Nederlander, Beitr. z. path. Anat. u. z. allg. Path. **73**: 313, 1925.
17. Hellwig, C. A.: The Geographic Pathology of Goiter, Surg., Gynec. & Obst. **55**: 35, 1932.
18. Idem: Morphogeographic and Experimental Studies on Etiology of Goiter, West. J. Surg. **41**: 453, 1933.
19. Turton, P. H. J.: The Distribution of Simple Goiter in Derbyshire, Proc. Roy. Soc. Med. **26**: 1223, 1933.
20. Smith, J. H.: Solar Radiation in Relation to Endemic Goiter, Arch. Int. Med. **50**: 76, 1932.
21. Idem: Etiology and Pathogenesis of Goiter, Virginia M. Monthly **60**: 90, 1933.
22. Bircher, E.: Das Kropfproblem, Beitr. z. klin. Chir. **89**: 1, 1914.
23. Waller, H. E.: The Relationship of the Thyroid Gland to Other Internal Secretions of Sexual Origin, Practitioner **89**: 279, 1912.
24. Hellwig, C. A.: Iodine Deficiency and Goiter, Arch. Path. **11**: 709, 1931.
25. Hibbard, James S.: Experimental Thyroid Hyperplasia: An Increased Intake of Chloride Combined With a Diet Deficient in Iodine as a Factor, Arch. Surg. **26**: 648, 1933.
26. Thompson, J.: Influence of Intake of Calcium on Thyroid Gland of Albino Rat, Arch. Path. **16**: 211, 1933.
27. Warthin, A. S.: The Constitutional Entity of Exophthalmic Goiter and So-Called Toxic Adenoma, Ann. Int. Med. **2**: 553, 1928.

28. Cannon, W. B., Binger, C. A. L., and Fitz, R.: Experimental Hyperthyroidism, Am. J. Physiol. **36**: 363, 1914-15.
29. Wilson, L. B.: Experimental Lesions in the Cervical Sympathetic Ganglia in Relation to Exophthalmic Goiter, Am. J. Med. Sc. **156**: 553, 1918.
30. Marine, D., Rogoff, J. M., and Stewart, G. M.: The Influence on the Thyroid of Anastomosis of the Phrenic and Cervical Sympathetic Nerves, Am. J. Physiol. **45**: 268, 1918.
31. Reid, Mont R., and Holman, Cranston: Effect of Removal of Stellate Sympathetic Ganglion on Gross and Histologic Structure of the Thyroid Gland, Arch. Surg. **32**: 452, 1936.
32. Halsted, W. S.: An Experimental Study of the Thyroid Gland of Dogs, With Especial Consideration of Hypertrophy of This Gland, Johns Hopkins Hosp. Rep. **1**: 373, 1896.
33. Idem: Reconsideration of the Question of Experimental Hypertrophy of the Thyroid Gland and the Effect of Excision of This Organ on Other of the Ductless Glands, Am. J. Med. Sc. **147**: 56, 1914.
34. Cole, W. H., and Womack, N. A.: Reactions of Thyroid Gland to Infections in Other Parts of the Body, J. A. M. A. **92**: 453, 1929.
35. Womack, N. A., and Cole, W. H.: Normal and Pathologic Repair in the Thyroid Gland, Arch. Surg. **23**: 466, 1931.
36. Mahorner, H. R.: Attempts to Produce Hyperplasia of Thyroid Gland by Infection and by Injury to the Adrenal Gland, Proc. Soc. Exper. Biol. & Med. **30**: 770, 1933.
37. Plummer, W. A., and Mayo, Charles: Surgical Operations and Associated Infections as Possible Etiological Factors in the Development of Exophthalmic Goiter and of Hyperthyroidism From Adenomatous Goiter, Surg., Gynec. & Obst. **53**: 721, 1931.
38. Mittelmann, B.: Psychogenic Factors in Hyperthyreosis and Rapid Heart Action, J. Nerv. & Ment. Dis. **77**: 465, 1933.
39. Geyer, H.: Psychic Trauma in Pathogenesis of Goiter, Ztschr. f. klin. Med. **124**: 168, 1933.
40. Licini, C.: Der Einfluss der Exstipation des Pancreas auf die Schilddrüse, Deutsche Ztschr. f. Chir. **101**: 521, 1909.
41. Davis, J. S., Hinton, J. W., and Killian, J. A.: Disturbed Protein Metabolism as a Cause of Colloid Goiter in Dogs, West. J. Surg. **40**: 665, 1932.
42. Hinton, J. W., Morton, P. C., and Weeks, C.: Experimental and Clinical Studies of the Relationship of Thyroid Disease and Pancreatic Function, Ann. Surg. **99**: 126, 1934.
43. Marine, D., and Baumann, E. J.: Influence of Glands With Internal Secretion or Respiratory Exchange. Effect of Suprarenal Insufficiency (by Removal or Freezing) in Rabbits, Am. J. Physiol. **57**: 135, 1921.
44. Marine, D.: Etiology of Graves's Disease, Ann. Int. Med. **4**: 423, 1930.
45. Idem: Remarks on the Pathogenesis of Graves's Disease, M. Press **131**: 29, 1931.
46. Shapiro, S., and Marine, D.: Clinical Report of Case of Graves's Disease With Rapid Improvement Following Oral Administration of Fresh Ox Suprarenal Gland, Endocrinology **5**: 699, 1921.
47. Tsuji, K.: Etiology and Treatment of Exophthalmic Goiter, Acta scholae. med. univ. imp. in Kioto **5**: 329, 1922.
48. Crile, G. W.: Recurrent Hyperthyroidism, Neurocirculatory Asthenia, and Peptic Ulcer. Treatment by Operations on Suprarenal Sympathetic System, J. A. M. A. **97**: 1616, 1931.
49. Pemberton, John deJ.: Reactions Following Operations for Hyperthyroidism, Ann. Surg. **104**: 507, 1936.
50. Marine, D.: Further Observations and Experiments on Goiter (So-Called Thyroid Carcinoma) in Brook Trout, J. Exper. Med. **19**: 70, 1914.
51. Webster, B., and Chesney, A. M.: Studies in the Etiology of Simple Goiter, Am. J. Path. **6**: 275, 1930.
52. Webster, B., Marine, D., and Cipra, A.: Occurrence of Seasonal Variations in Goiter of Rabbits Produced by Feeding Cabbage, J. Exper. Med. **58**: 81, 1931.
53. Webster, B.: Production of Simple Goiter, Endocrinology **16**: 617, 1932.
54. Idem: Studies in the Experimental Production of Simple Goiter, Endocrinology **16**: 617, 1932.
55. McCarrison, R., Sankaran, G., and Madhava, K. B.: Effect of Exclusive Diet of Cabbage on Internal Organs of Rabbits With Statistical Examination of Data, Indian J. M. Research **20**: 723, 1933.

56. Westra, J. J., and Hunter, V.: Effect of Irradiating Non-Goiterogenic Cabbage on Its Goiterogenic Activity, Proc. Soc. Exper. Biol. & Med. **30**: 1157, 1933.
57. McCarrison, R.: Goiterogenic Action of Soya Bean and Groundnut, Indian J. M. Research **21**: 179, 1933.
58. Idem: The Etiology of Endemic Goiter, Milroy Lectures, London, 1913, John Bale, Sons & Danielsson, Ltd.
59. Idem: Interaction of Food and Sanitary Conditions in Causation of Thyroid Disease, Indian J. M. Research **20**: 957, 1933.
60. Idem: Experimental Production of Lymphadenoid Goiter, Brit. M. J. **1**: 5, 1929.
61. Idem: Food and Goiter, Brit. M. J. **2**: 671, 1933.
62. Spence, A. W.: Effect of Administration of Cyanides on Thyroid Gland of Chickens, J. Pharmacol. & Exper. Therap. **48**: 327, 1933.
63. Cole, W. G., Womack, N. A., and Ellett, W. H.: The Production of Hyperplasia of the Thyroid Gland by Chemical Means, With Special Reference to Purine Bases and Their Derivatives, Arch. Surg. **22**: 926, 1931.
64. Marine, D., and Rosen, S. H.: Exophthalmos in Thyroidectomized Guinea Pigs by Thyrotropic Substances of Anterior Pituitary and the Mechanism Involved, Proc. Soc. Exper. Biol. & Med. **30**: 901, 1933.
65. Simpson, S., and Hunter, A.: The Possible Vicarious Relationship Between the Pituitary and Thyroid Glands, Quart. J. Exper. Physiol. **3**: 121, 1910; also **4**: 257, 1911.
66. Benedict, F. G., and Homans, J.: The Metabolism of the Hypophysectomized Dog, J. Med. Research **25**: 409, 1911-12.
67. Gudernatsch, J. F.: Feeding Experiments on Tadpoles. II. A Further Contribution to the Knowledge of Organs of Internal Secretion, Am. J. Anat. **15**: 431, 1914.
68. Smith, P. E.: Experimental Ablation of the Hypophysis in the Frog Embryo, Science **44**: 280, 1916.
69. Allen, B. M.: The Results of Extirpation of the Anterior Lobe of the Hypophysis and of the Thyroid of Rana Pipiens Larvae, Science **44**: 755, 1916.
70. Idem: Experiments in Transplantation of the Hypophysis of Adult Rana Pipiens to Tadpoles, Science **52**: 274, 1920.
71. Smith, P. E., and Smith, I. P.: The Repair and Activation of the Thyroid in the Hypophysectomized Tadpole by the Parenteral Administration of Fresh Anterior Lobe of the Bovine Hypophysis, J. Med. Research **43**: 267, 1922.
72. Shockaert, J. A.: Hyperplasia of Thyroid and Exophthalmus From Treatment With Anterior Pituitary in Young Duck, Proc. Soc. Exper. Biol. & Med. **29**: 306, 1931.
73. Collip, J. B., and Anderson, E. M.: The Production of Serum Inhibitory to the Thyrotropic Hormone, Lancet **1**: 76, 1934.
74. Anderson, E. M., and Collip, J. B.: Preparation and Properties of an Antithyrotropic Substance, Lancet **1**: 784, 1934.
75. Thompson, W. O., Taylor, S. G., Thompson, T. K., Nadler, S. C., and Dicky, F. L. N.: The Calorigenic Action of Extract of the Anterior Lobe of the Pituitary in Man, Endocrinology **20**: 55, 1936.
76. Foster, G. L., and Smith, P. E.: Hypophysectomy and Replacement Therapy in Relation to Basal Metabolism and Specific Dynamic Action in the Rat, J. A. M. A. **87**: 2151, 1926.
77. Uhlenhuth, E., and Schwartzbach, S. S.: Control of the Thyroid Function by the Anterior Lobe of the Hypophysis, Anat. Rec. **34**: 119, 1926.
78. Idem: Anterior Lobe Substance, the Thyroid Stimulator. I. Induces Precocious Metamorphosis, Proc. Soc. Exper. Biol. & Med. **26**: 149, 1928.
79. Idem: Anterior Lobe Substance, the Thyroid Stimulator. III. The Effect of Anterior Lobe Substance on the Thyroid Gland, Proc. Soc. Exper. Biol. & Med. **26**: 152, 1928.
80. Idem: Anterior Lobe, the Thyroid Activator, Anat. Rec. **42**: 41, 1929.
81. Aron, M.: Action de la prehypophyse sur le thyroïde chez le cobaye, Compt. rend. Soc. de Biol. **102**: 682, 1929.
82. Idem: Particularites histologique de la réaction de la thyroïde aux extraits de lobe antérieur d'hypophyse, Compt. rend. Soc. de Biol. **103**: 145, 1930.

83. Idem: Indications apportées par la méthode des injections hypophysaires sur le functionnement de la thyroïde et ses tests morphologique, Compt. rend. Soc. de Biol. **103**: 148, 1930.
84. Idem: Sur la spécificité du principe excito-secréteur de la thyroïde renfermé dans les extraits de prehypophyse, Compt. rend. Soc. de Biol. **105**: 974, 1931.
85. Anderson, E. M., and Collip, J. B.: Thyrotropic Hormone of the Anterior Pituitary, Proc. Soc. Exper. Biol. & Med. **30**: 680, 1933.
86. Anderson, E. M.: Production of Hyperplasia of Thyroid With Hyperthyroidism in Albino Rat, Canad. M. A. J. **28**: 23, 1933.
87. Anderson, E. M., and Collip, J. B.: Studies on the Physiology of the Thyrotropic Hormone of the Anterior Pituitary, J. Physiol. **82**: 11, 1934.
88. Black, P. T., Collip, J. B., and Thomson, D. L.: The Effect of Anterior Pituitary Extracts on Acetone Body Excretion in the Rat, J. Physiol. **82**: 385, 1934.
89. Schwartzbach, S. S., and Uhlenhuth, E.: Anterior Lobe Substance, the Thyroid Stimulator. IV. Effect in Absence of Thyroid Gland, Proc. Soc. Exper. Biol. & Med. **26**: 153, 1928.
90. Idem: Effect of Anterior Lobe Substance on Basal Metabolism in Salamander Larvae, Anat. Rec. **41**: 25, 1928.
91. Idem: Anterior Lobe and Basal Metabolism, Anat. Rec. **42**: 35, 1929.
92. Shockaert, J.: À propos de l'action stimulante des extraits prehypophysaires sur la thyroïde, Compt. rend. Soc. de Biol. **105**: 223, 1930.
93. Shockaert, J. A., and Foster, G. L.: Influence of Anterior Pituitary Substances on the Total Iodine Content of the Thyroid Gland in the Young Duck, J. Biol. Chem. **95**: 89, 1932.
94. Silverberg, M.: Effects of Combined Administration of Extracts of Anterior Lobe of Pituitary and of Potassium Iodide on Thyroid Gland, Proc. Soc. Exper. Biol. & Med. **27**: 166, 1929.
95. Lee, M. O., and Gagnon, J.: The Effects of Growth Promoting and Gonad Stimulating Principles of the Anterior Lobe of the Pituitary on Basal Gaseous Metabolism in the Rat, Endocrinology **14**: 233, 1930.
96. Loeser, A.: Hypophysenvordenlappen und Jodgehalt der Schilddrüse, Arch. f. exper. Path. u. Pharmakol. **163**: 530, 1931.
97. Janssen, S., and Loeser, A.: Die Wirkung des Hypophysenvorderlappens auf die Schilddrüse, Arch. f. exper. Path. u. Pharmakol. **163**: 517, 1931.
98. Loeser, A.: Die Darslettung thyreotrop wirksomer Extrakte aus Hypophysenvorderlappen, Arch. f. exper. Path. u. Pharmakol. **166**: 693, 1932.
99. Idem: The Alteration of Thyroid Gland Activity by Means of Iodine, Klin. Wchnschr. **13**: 533, 1934.
100. Eitel, H., aand Loeser, A.: The Anterior Lobe of the Pituitary Gland, the Thyroid Gland, and the Carbohydrate Metabolism of the Liver, Internat. Clin. **2**: 66, 1934.
101. Loeb, L., and Bassett, R. B.: Effect of Hormone of Anterior Pituitary on Thyroid Gland in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **26**: 860, 1929.
102. Idem: Comparison of Effects of Various Preparations of Anterior Pituitary Gland on Thyroid of Guinea Pig, Proc. Soc. Exper. Biol. & Med. **27**: 490, 1930.
103. Loeb, L., Bassett, R. B., and Friedman, H.: Further Investigations Concerning the Stimulating Effect of Anterior Pituitary Gland Preparation on the Thyroid Gland, Proc. Soc. Exper. Biol. & Med. **28**: 209, 1930.
104. Loeb, L., and Friedman, H.: Long Continued Injections of Acid Extract of Anterior Pituitary on Thyroid Gland and Sex Organs, Proc. Soc. Exper. Biol. & Med. **29**: 172, 1931.
105. Loeb, L., and Friedman, H.: Exophthalmos Produced by Injection of Acid Extract of Anterior Pituitary Gland of Cattle, Proc. Soc. Exper. Biol. & Med. **29**: 648, 1932.
106. Grant, M. P.: The Release of Follicular Colloid From the Thyroid of Necturus Maculosus Following Heteroplastic Anterior Pituitary Implants, Anat. Rec. **46**: 205, 1930.
107. Idem: The Release of Follicular Colloid From the Thyroid of Necturus Maculosus Following Heteroplastic Anterior Pituitary Implants, Anat. Rec. **49**: 373, 1931.
108. Verzár, F., and Wahl, W.: Wirkung des Hypophysenvorderlappen-hormons auf den O_2-Verbrauch von Meerschweinchen, Biochem. Ztschr. **240**: 37, 1931.

109. Grab, W.: Hypophysenvorderlappen und Schilddrüse. Der Jodgehalt des Blutes und der Schilddrüse nach Zufuhr von Hypophysenvorderlappenstoffen, Arch. f. exper. Path. u. Pharmakol. **167**: 413, 1932.
110. Idem: Die Wirkung des Hypophysenvorderlappens auf die Schilddrüsenfunktion, Arch. f. exper. Path. u. Pharmakol. **167**: 103, 1932.
111. Idem: Hypophysenvorderlappen und Schilddrüse. Die Wirkung des Hypophysenvorderlappens auf die Lätigkiet der Schilddrüse, Arch. f. exper. Path. u. Pharmakol. **167**: 313, 1932.
112. Foster, G. L., Gutman, A. B., and Gutman, E. B.: Total and Thyroxin Iodine Content of Thyroid Gland After Injection of Saline Anterior Pituitary Extracts, Proc. Soc. Exper. Biol. & Med. **30**: 1028, 1933.
113. Eitel, H., and Loeser, A.: Hypophysenvorderlappen, Schilddrüse und Kohlehydratstoffwechsel der Leber, Arch. f. exper. Path. u. Pharmakol. **167**: 381, 1932.
114. Closs, K., Loch, L., and MacKay, E. M.: The Effect of an Acid Extract of the Anterior Pituitary on the Iodine Concentration of the Blood and Thyroid Gland, J. Biol. Chem. **96**: 585, 1932.
115. Siebert, W. J., and Smith, R. S.: Effect of Various Anterior Pituitary Preparations on Basal Metabolism in Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **27**: 622, 1930.
116. Idem: The Effect of Various Anterior Pituitary Preparations Upon Basal Metabolism in Partially Thyroidectomized and in Completely Thyroidectomized Guinea Pigs, Am. J. Physiol. **95**: 396, 1930.
117. Siebert, W. J., and Thurston, E. W.: Basal Metabolism After K. I. With Acid Extract of Anterior Pituitary Glands, Pituitary Tablets, and With Thyroid, Proc. Soc. Exper. Biol. & Med. **29**: 652, 1932.
118. Thurston, E. W.: A Comparison of Hypertrophic Changes in Thyroid Caused in Different Species by Acid Extract of the Anterior Lobe of the Bovine Pituitary Gland, Arch. Path. **15**: 67, 1933.
119. Benedict, E. B., Putnam, T. J., and Teel, H. M.: Early Changes Produced in Dogs by Injections of Sterile Active Extract From Anterior Lobe of Hypophysis, Am. J. Med. Sc. **179**: 489, 1930.
120. Junkmann, K., and Schoeller, W.: Ueber das thyreotrope Hormon des Hypophysenvorderlappens, Klin. Wchnschr. **11**: 1176, 1932.
121. Greep, R.: Effect of Luteinizing and Follicular Stimulating Fractions of Pituitary on Thyroid, Proc. Soc. Exper. Biol. & Med. **30**: 1362, 1933.
122. Hageman, P. O., and McCordock, H. A.: Effect of Acid Extract of Anterior Pituitary on Heart Rate and Nervous Irritability of Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **30**: 297, 1933.
123. Houssay, B. A.: The Influence of the Pituitary on the Basal Metabolism and on Specific Dynamic Action, Endocrinology **18**: 409, 1934.
124. Doederlein, G.: Weiter Experimentelle Untersuchungen über die Wirkung des thyreotropen Hormons des Hypophysenvorderlappen, Arch. f. Gynäk. **115**: 22, 1933.
125. Kendall, E. C.: The Thyroid Hormone, Collec. Papers Mayo Clin. **9**: 309, 1917.
126. Harington, C. R.: Chemistry of Thyroxine: Constitution and Synthesis of Desiodo-Thyroxine, Biochem. J. **20**: 300, 1926.
127. Idem: The Biochemical Basis of Thyroid Function, Lancet **2**: 1261, 1935.
128. Abelin, I.: Einfluss des Dijod-tyrosins auf den hyperthyreotischen Stoffwechsel, Biochem. Ztschr. **233**: 483, 1931.
129. Delcourt-Bernard, E.: Étude expérimentale de l'action de la 3.5 di-iodotyrosine dans le traitement de l'hyperthyroidie, Rev. belge sc. méd. **6**: 1, 1934.
130. Lerman, J., and Salter, W. T.: The Calorigenic Action of Thyroid and Some of Its Active Constituents, Endocrinology **18**: 317, 1934.
131. Marine, D., and Lenhart, C. H.: Relation of Iodin to the Structure of Human Thyroids, Arch. Int. Med. **4**: 440, 1909.
132. Mosser, W. B.: The Effect of Iodine and Thyroid Feeding on the Histology of the Gland of the Dog, Am. J. Surg. **7**: 338, 1929.
133. Jordi, A.: The Biological Value, Iodine Content, Histological Structure, and Clinical Picture of Goiter, Arch. Int. Med. **49**: 541, 1932.
134. Rienhoff, W. F.: Diseases of the Thyroid Gland, Dean Lewis System of Surgery, Vol. VI, Chapter 1, Hagerstown, Md., 1930, W. F. Prior Company, Inc.
135. Curtis, G. M.: The Iodine Relationships of Thyroid Disease, Surg., Gynec. & Obst. **62**: 365, 1936.

136. Plummer, H. S., and Boothby, W. M.: The Value of Iodine in Exophthalmic Goiter, Collec. Papers Mayo Clin. **15**: 565, 1923.
137. Boothby, W. M.: Diseases of the Thyroid Gland: An Interpretive Review of Progress Toward Solution of the Problem, Arch. Int. Med. **56**: 136, 1935.
138. Plummer, H. S., and Boothby, W. M.: The Value of Iodine in Exophthalmic Goiter, J. Iowa M. Soc. **14**: 66, 1924.
139. Graham, A., and Cutler, E. A.: Exophthalmic Goiter and Toxic Adenoma: Similarity of Response to Iodine, Ann. Surg. **84**: 497, 1926.
140. Thompson, W. O., Thompson, P. K., Brailey, A. G., and Cohen, A. C.: Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, Arch. Int. Med. **45**: 481, 1930.
141. Jackson, A. S., and Ewell, G. H.: Danger of Prolonged Use of Lugol's Solution With Case Reports and Study of Pathology, Am. J. Surg. **10**: 475, 1930.
142. Delcourt-Bernard, E.: Nouvelles recherches concernant l'action de l'iode sur le metabolisme de base, Rev. belge sc. méd. **4**: 503, 1932.
143. Harington, C. R., Gardiner-Hill, H., and Dunhill, T. P.: Discussion on the Use of Iodine Compounds in the Treatment of Thyroid Disease, Proc. Roy. Soc. Med. **26**: 870, 1933.
144. Winkenwerder, W. L., and McEachern, D.: The Use of Iodine in the Preoperative Treatment of Hyperthyroidism; With Remarks on Iodine Remissions as Observed in Baltimore, Maryland, Bull. Johns Hopkins Hosp. **51**: 282, 1932.
145. McClure, R. D.: Thyroid Surgery as Affected by the Generalized Use of Iodized Salt in an Endemic Goiter Region, Ann. Surg. **100**: 924, 1934.
146. Goetsch, E.: Correct and Incorrect Use of Iodine in the Treatment of Goiter, Am. J. Surg. **26**: 417, 1934.
147. De Quervain, F.: L'iode dans la physiologie et la pathologie de la thyroïde, Presse méd. **44**: 649, 1936.
148. Thompson, W. O., and Thompson, P. K.: Exophthalmic Goiter: The Development of Refractoriness to Iodine, Arch. Int. Med. **48**: 351, 1931.
149. Means, J. H.: Therapeutics of the Thyroid, J. A. M. A. **105**: 24, 1935.
150. Aitken, H. A. A.: An Improved Method for the Determination of Iodine in Blood, Biochem. J. **24**: 1456, 1930.
151. Perkin, H. J., Brown, B. R., and Lang, J.: The Blood-Iodine Content of Normal and Thyrotoxic Individuals; Iodine-Tolerance Test, Canad. M. A. J. **31**: 365, 1934.
152. Lahey, F. H.: Stage Operations in Severe Hyperthyroidism, Ann. Surg. **104**: 961, 1936.
153. Watson, E. M.: An Iodine-Tolerance Test for the Investigation of Thyroid Function, Endocrinology **20**: 358, 1936.
154. Sandiford, Irene: The Basal Metabolic Rate in Exophthalmic Goiter With a Brief Description of the Technic, Endocrinology **4**: 71, 1920.
155. Boothby, W. M.: The Basal Metabolic Rate in Hyperthyroidism, J. A. M. A. **77**: 252, 1921.
156. Jenkins, R. L.: Basal Metabolism. I. The Error of Basal Metabolism Determination and the Normal Range of Basal Metabolism. II. The Basal Pulse Complex, Arch. Int. Med. **49**: 181, 188, 1932.
157. Goetsch, E.: Newer Methods in the Diagnosis of Thyroid Disorders, Pathological and Clinical, New York State J. Med. **18**: 259, 1918.
158. Carmona, L.: Sulla reazione di Kottmann, Clin. chir. **8**: 1057, 1932.
159. Brazier, M. A. B., and Grant, F. M.: The Relation of the Impedance-Angle Test of Thyrotoxicosis in Changes in the Basal Metabolism, Lancet **2**: 125, 1934.
160. Brazier, M. A. B.: The Impedance Angle Test for Thyrotoxicosis. Part I. Technic and Study of Normals, West. J. Surg. **43**: 429, 1935.
161. Idem: The Impedance Angle Test for Thyrotoxicosis. Part II. Application in Diagnosis of Thyroid Disease, West. J. Surg. **43**: 514, 1935.
162. Robertson, J. D., and Wilson, A. T. A.: A Combined Study of Basal Metabolism and Impedance Angle in Thyrotoxicosis and Myxedema, Lancet **2**: 1158, 1934.
163. Horton, J. W., et al.: The Clinical Significance of Electrical Impedance Determination in Thyroid Disorders, Endocrinology **20**: 72, 1936.
164. Hurzthal, L. M., and Hunt, H. M.: Clinical Relationships of Blood Cholesterol With a Summary of Our Present Knowledge of Cholesterol Metabolism, Ann. Int. Med. **9**: 717, 1935.

165. McGee, L. C.: The Blood Cholesterol in Disturbances of the Basal Metabolic Rate, Ann. Int. Med. **9**: 728, 1935.
166. Marine, D.: The Physiology of the Normal Thyroid and the Physiology of the Thyroid in Exophthalmic Goiter, Ohio State M. J. **16**: 735, 1920.
167. Boothby, W. M.: The Thyroid Problem, Collec. Papers Mayo Clin. **20**: 495, 1928.
168. Richter, C. P.: The Rôle Played by the Thyroid Gland in the Production of Gross Body Activity, Endocrinology **18**: 73, 1933.
169. Kosdoba, A.: Ueber einige Probleme der klinischen Chirurgie und der experimentellen Endokrinopathologie, Arch. f. klin. Chir. **182**: 414, 1935.
170. Galli, R.: Tiroidectomie e decorso delle infezioni. Studio morfologico delle reazoni cellulari negli animale stiroidati, Arch. ital. di chir. **41**: 571, 1935.
171. Mahorner, H. R., et al.: Observations on the Lymphatic Connections of the Thyroid Gland in Man, Anat. Rec. **36**: 341, 1927.
172. Chouke, K. S., Whitehead, R. M., and Parker, A. E.: Is There a Closed Lymphatic System Connecting the Thyroid and Thymus Glands? Surg., Gynec. & Obst. **54**: 865, 1932.
173. Rienhoff, W. F., Jr.: The Lymphatic Vessels of the Thyroid Gland in the Dog and in Man, Arch. Surg. **23**: 783, 1931.
174. Halsted, W. S.: The Significance of the Thymus Gland in Graves's Disease, Harvey Lectures, 1913-14, Philadelphia and London, J. B. Lippincott Company **9**: 224, 1915.
175. Briane, J., and Funck-Brentano, P.: Les variations der artères du corps thyroïde. Étude d'anatomie chirurgicale, Ann. d'anat. path. **40**: 125, 1934.
176. Berlin, D. D., and Lahey, F. H.: Dissections of the Recurrent and Superior Laryngeal Nerves, Surg., Gynec. & Obst. **49**: 102, 1929.
177. Berlin, D. D.: The Recurrent Laryngeal Nerves in Total Ablation of the Normal Thyroid Gland, Surg., Gynec. & Obst. **60**: 19, 1935.
178. Lahey, F. H.: The Effect of Thyroid Pressure Upon the Trachea, S. Clin. North America **2**: 459, 1931.
179. Schindler, C.: Ueber trachealstenosen mit besonderer Beruecksichtigung der durch Kropfbedingten, Jahresk. ärztl. Fortbild. **26**: 1, 1935.
180. New, G. B., and Childrey, J. H.: Paralysis of the Vocal Cords: A Study of 217 Medical Cases, Arch. Otolaryng. **16**: 143, 1932.
181. Hoover, W. B.: Bilateral Abductor Paralysis: Operative Treatment by Submucous Resection of the Vocal Cords, Arch. Otolaryng. **15**: 339, 1932.
182. Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter, Arch. Int. Med. **8**: 265, 1911.
183. Wilson, L. B., and Kendall, E. C.: The Relationship of the Pathological Histology and the Iodine Compounds of the Human Thyroid, Am. J. M. Sc. **151**: 79, 1916.
184. Zechel, G.: Follicular Destruction in the Normal Thyroid of the Dog; With a Consideration of the Relation Between Follicles and Interfollicular Cells, Surg., Gynec. & Obst. **52**: 228, 1931.
185. Idem: Cellular Studies of the Thyroid Gland, Surg., Gynec. & Obst. **54**: 1, 1932.
186. Rice, Carl O.: Incidence of Nodules in the Thyroid, Arch. Surg. **24**: 505, 1932.
187. Hellwig, C. A.: Graves's Constitution (Warthin), Surg., Gynec. & Obst. **52**: 43, 1931.
188. Markowitz, B.: Life Cycle of Thyroid Cell and Its Relation to Goiter, West. J. Surg. **41**: 463, 1933.
189. Roussy, G., Huguenis, R., and Welti, H.: Structure histologique de la thyroïde restante après guérison de la maldie de Basedow par thyroïdectomie subtotale, Ann. d'anat. path. **11**: 555, 1934.
190. Rabinovitch, J., Pearson, J. R., and Louria, H. W.: A Clinical, Pathologic, and Experimental Study of the Structural Relationship of Goiter, Endocrinology **19**: 383, 1935.
191. Hertzler, A. E.: Diseases of the Thyroid Gland, ed. 2, St. Louis, 1929, The C. V. Mosby Company.
192. Keilty, R. A.: Inflammatory Nature of Nodular Goiter as a Chronic Thyroiditis, Am. J. Clin. Path. **1**: 57, 1931.
193. Simpson, W. M.: Graves's Constitution (Warthin), Am. J. Surg. **7**: 22, 1929.
194. Van Meter, S. D.: The Classification of Goiter, Northwest. Med. **29**: 404, 1930.

195. Standard Classified Nomenclature of Disease, New York, The Commonwealth Fund, 1935.
196. Blackford, J. M., and Freligh, W. P.: The Thymus in Adults, With Especial Reference to Goiter, Collec. Papers Mayo Clin. **8**: 507, 1916.
197. Margolis, H. M.: The Possible Significance of the Thymus Gland in the Syndrome of Hyperthyroidism, Ann. Int. Med. **4**: 1112, 1931.
198. McEachern, D., and Rake, G.: A Study of the Morbid Anatomy of the Hearts From Patients Dying With Hyperthyroidism, Bull. Johns Hopkins Hosp. **48**: 273, 1931.
199. Rake, G., and McEachern, D.: Experimental Hyperthyroidism and Its Effect Upon the Myocardium in Guinea Pigs and Rabbits, J. Exper. Med. **54**: 23, 1931.
200. Parenti, G. C., and Poloni, P.: Le reazioni istologische della muscolatura scheletrica nella tireotossicosi sperimentale, Sperimentale, Arch. di biol. **89**: 485, 1935.
201. Meyer, H. W.: Congenital Cysts and Fistulae of the Neck, Ann. Surg. **95**: 226, 1932.
202. Graham, A., and McCullagh, E. P.: Atrophy and Fibrosis Associated With Lymphoid Tissue in the Thyroid: Struma Lymphomatosa (Hashimoto), Arch. Surg. **22**: 548, 1931.
203. Nestmann, F.: Zur Frage der chronischen Thyreoiditis, Beitr. z. klin. Chir. **156**: 253, 1932.
204. Rankin, F. W., and Graham, A. S.: Tuberculosis of the Thyroid Gland, Ann. Surg. **96**: 625, 1932.
205. Clute, J. M., and Lahey, F. H.: Thyroiditis, Ann. Surg. **95**: 493, 1932.
206. Boyden, A. M., Coller, F. A., and Bugher, J. C.: Riedel's Struma, West. J. Surg. **43**: 547, 1935.
207. Lahey, Frank H.: Thyroiditis; An Operative Procedure for the Relief of Tracheal Constriction Due to Thyroiditis, Surg., Gynec. & Obst. **60**: 969, 1935.
208. Habershon, S. O.: Exophthalmic Goiter; Heart Disease; Jaundice, Death, Lancet **1**: 510, 1874.
209. Sutcliff, E. H.: An Extraordinary Acute Case of Graves's Disease, Lancet **1**: 717, 1898.
210. Eder, M. D.: Three Cases of Jaundice Occurring in Persons Suffering From Exophthalmic Goiter, Lancet **1**: 1758, 1906.
211. Kohn, L. Winfield: Gastro-Intestinal Symptoms in Disturbances of the Thyroid, New York State J. Med. **110**: 1066, 1919.
212. Kerr, W. J., and Rusk, G. U.: Acute Yellow Atrophy Associated With Hyperthyroidism, M. Clin. North America **6**: 445, 1922.
213. Kerr, W. J.: Necrosis of Heart and Liver in Thyrotoxicosis With Some Notes on Possible Changes in Other Organs, Northwest Med. **29**: 430, 1930.
214. Crotti, André: Thyroid and Thymus, Philadelphia, 1922, Lea & Febiger.
215. Weller, C. V.: Hepatic Lesions Associated With Exophthalmic Goiter, Tr. A. Am. Physicians **45**: 71, 1930.
216. Assmann, H.: Leber und Milz bei Morbus Basedow, München. med. Wchnschr. **78**: 221, 1931.
217. Lewis, W.: Hyperthyroidism and Associated Pathology, Am. J. M. Sc. **181**: 65, 1931.
218. Beaver, D. C., and Pemberton, J. deJ.: The Pathologic Anatomy of the Liver in Exophthalmic Goiter, Ann. Int. Med. **7**: 687, 1933.
219. Mahorner, H. R.: Jaundice Associated With Hyperthyroidism, New Orleans M. & S. J. **87**: 382, 1934.
220. Youmans, J. B., and Warfield, L. M.: Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency, Arch. Int. Med. **37**: 1, 1926.
221. Kuriyama, S.: The Influence of Thyroid Feeding Upon Carbohydrate Metabolism. I. The Storage and Mobilization of the Liver Glycogen in Thyroid Fed Animals, J. Biol. Chem. **33**: 193, 1918.
222. Maes, U., Boyce, F. F., and McFetridge, Elizabeth M.: Further Observations on Thyroid Disease in a Non-Endemic Area, Ann. Surg. **105**: 700, 1937.
223. Graham, Allen: Malignant Tumors of the Thyroid: Epithelial Types, Ann. Surg. **82**: 30, 1925.
224. Clute, H. M., and Warren, S.: Cancer of the Thyroid Gland, Am. J. Cancer **15**: 2563, 1931.

225. Pemberton, John deJ.: Malignant Disease of the Thyroid Gland. A Clinical Consideration, Ann. Surg. **87**: 369, 1928.
226. Dinsmore, R. S., and Crile, G., Jr.: Thyroid Problems and End-Results of Operations on the Thyroid Gland, S. Clin. North America **15**: 859, 1935.
227. Smith, L. W., Pool, E. H., and Olcott, C. T.: Malignant Disease of the Thyroid Gland, Clinicopathologic Analysis of 54 Cases of Thyroid Malignancy, Am. J. Cancer **20**: 1, 1934.
228. Breitner, B.: Neoplasms of the Thyroid, Wien. klin. Wchnschr. **2**: 1169, 1931.
229. Sutherland, C. G., Decker, F. H., and Cilley, E. I. L.: Metastatic Malignant Lesions in Bone, Am. J. Cancer **16**: 1457, 1932.
230. Copeland, M. M.: Skeletal Metastases Arising From Carcinoma and From Sarcoma, Arch. Surg. **23**: 581, 1931.
231. Engelstadt, R. E.: The Thyroxin Production in Metastases From Carcinoma of the Thyroid, Am. J. Cancer **26**: 738, 1936.
232. Pack, G. T., and Craver, L. F.: Tumors of the Larynx and Thyroid: A Roentgenographic Study, Arch. Otolaryng. **13**: 658, 1931.
233. Mulvihill, D. A.: A Contribution on Malignant Tumors of the Thyroid, Deutsche Ztschr. f. Chir. **244**: 71, 1934.
234. Schreiner, B. F., and Murphy, W. T.: Malignant Neoplasms of the Thyroid Gland, Ann. Surg. **99**: 116, 1934.
235. Stewart, S. W.: Radiosensitivity of Tumors, Arch. Surg. **27**: 979, 1933.
236. De Quervain, F.: Zur Diagnose und Therapie der Struma Maligna, Bull. Schweiz. Ver. igg. Krebsbekpfg. **1**: 273, 1934.
237. Dunhill, T. P.: Carcinoma of the Thyroid Gland, Brit. J. Surg. **19**: 83, 1931.
238. Clute, H. M., and Warren, S.: Prognosis of Thyroid Cancer, Surg., Gynec. & Obst. **60**: 861, 1935.
239. Bowing, H. H.: Malignant Tumors of the Thyroid Gland Treated by Operation, Radium, and Roentgen Rays, Collec. Papers Mayo Clin. **19**: 578, 1927.
240. Zuppinger, A., and Rohrer, C.: Zur Klinik und Therapie der Struma Maligna Bericht über 101 Fälle, von 1918-1933, Acta radiol. **15**: 523, 1934.
241. Crile, George, and Crile, George, Jr.: A Radical Operation for Malignant Tumors of the Thyroid Gland, Surg., Gynec. & Obst. **64**: 921, 1937.
242. Cattell, R. B.: Aberrant Thyroid, J. A. M. A. **97**: 1761, 1931.
243. Lazarus, J. A., and Rosenthal, L. A. A.: Lateral Aberrant Thyroid Glands, Ann. Surg. **98**: 1023, 1933.
244. Valdoni, P.: Metastasi endogugulare da progresso tumore della tiroide, Arch. ital. di chir. **32**: 749, 1932.
245. Hertzler, A. E.: Pathogenesis of Goiter Considered as One Continuous Disease Process, Arch. Surg. **16**: 61, 1928.
246. Wendel, A.: Chronic Thyroid Disease, One Continuous Disease Process, Am. J. Surg. **21**: 446, 1933.
247. Bram, L.: Toxic Adenoma and Graves's Disease: Comments Based on Series of 11,000 Goiter Cases, Northwest Med. **28**: 210, 1929.
248. Fortune, C. H.: A Clinical Study of the Graves's Constitution and Its Relation to Thyroid Disease, Ann. Int. Med. **6**: 869, 1933.
249. Roeder, C. A., and Killins, W. A.: Third Type of Toxic Thyroidism, Northwest Med. **29**: 395, 1930.
250. Pemberton, John deJ., and Haines, Samuel F.: Diseases of the Thyroid and Their Management, Christopher's Textbook of Surgery, Chap. II, p. 213, Philadelphia, 1936, W. B. Saunders Company.
251. Mahorner, Howard R.: Clinical Aspects of Goiter, New Orleans M. & S. J. **89**: 673, 1937.
252. Hill, H. G.: Primary Graves's Disease With Especial Reference to Sex Events of Females, Quart. J. Med. **22**: 217, 1929.
253. Meldolesi, G.: La funzione mestruale nella malatta Flajani-Basedow, Policlinico (sez. med.) **38**: 620, 1931.
254. Mussey, R. D., Plummer, W. A., and Boothby, W. M.: Pregnancy Complicating Exophthalmic Goiter and Adenomatous Goiter With Hyperthyroidism, Collec. Papers Mayo Clin. **18**: 544, 1926.
255. Bothe, F. A.: Hyperthyroidism Associated With Pregnancy, Am. J. Obst. & Gynec. **25**: 628, 1933.
256. Helmholz, H. F.: Exophthalmic Goiter in Childhood, J. A. M. A. **87**: 157, 1926.
257. McGraw, A. B.: Juvenile Goiter, Surg., Gynec. & Obst. **47**: 25, 1928.

258. Cattell, R. B.: Thyroid Disorders in Childhood, New England J. Med. **209**: 867, 1933.
259. Duncan, W. S.: The Relationship of Thyroid Disease to Chronic Non-Specific Arthritis, J. A. M. A. **99**: 1239, 1932.
260. Cohen, S. J., and King, F. H.: The Relation Between Myasthenia Gravis and Exophthalmic Goiter, Arch. Neurol. & Psychiat. **28**: 1338, 1932.
261. Mussio-Fournier, J. C., et al.: Familial Infantilism Due to Hypophyseal and Thyroid Insufficiency, Endocrinology **18**: 533, 1934.
262. Dunlap, H. F., and Kepler, E. J.: A Syndrome Resembling Familial Periodic Paralysis Occurring in the Course of Exophthalmic Goiter, Endocrinology **15**: 541, 1931.
263. Bing, J.: Die genotypisch bedingte sporadische Strume—Kropf—und deren Verhalten zu anderen Thyreoidea-Leiden, Acta med. Scandinav. **79**: 298, 1932.
264. Pascual, E. O., Montejo, S., and Galán, A.: Tiroides y recambia hemoglobinico, Méd. ibera **16**: 973, 1932.
265. Friedgood, H. B.: The Effect of Lugol's Solution on Chronic Lymphatic Leukemia and Its Bearing Upon the Pathogenesis of Exophthalmic Goiter, Am. J. Med. Sc. **183**: 515, 1932.
266. Hubble, D.: The Influence of the Endocrine System in Blood Disorders, Lancet **2**: 113, 1933.
267. Golden, R., and Abbott, H.: The Relation of the Thyroid, the Adrenals and the Islands of Langerhans to Malacic Disease of Bone, Am. J. Roentgenol. **30**: 641, 1933.
268. Cohen, M. H.: Leg Ulcers Due to Thyroid Dysfunction, J. A. M. A. **102**: 283, 1934.
269. Hatlehol, R.: On Carbohydrate Metabolism in Thyrotoxicosis and Hypothyrosis, Acta med. Scandinav. **77**: 558, 1932.
270. John, H. J.: Hyperthyroidism Showing Carbohydrate Metabolism Disturbances: Ten Years' Study and Follow-Up of Cases, J. A. M. A. **99**: 620, 1932.
271. Wilder, R. M., Foster, R. F., and Pemberton, John deJ.: Total Thyroidectomy in Diabetes Mellitus, Endocrinology **18**: 455, 1934.
272. Womack, N. A., and Cole, W. H.: The Thyroid Gland in Hypoglycemia, Ann. Surg. **105**: 370, 1937.
273. Verbryeke, J. R., Jr.: Masked Gastro-Intestinal Hyperthyroidism: Report of Thirty-Four Cases, J. A. M. A. **97**: 513, 1931.
274. Parkinson, J., and Hoyle, C.: Thyrotoxic Hypertension, Lancet **2**: 913, 1934.
275. Towers, J. R. H.: Masked Hyperthyroidism as a Cause of Heart Disease, Lancet **1**: 67, 1933.
276. Pemberton, John deJ., and Willius, F. A.: Cardiac Features of Goiter, Ann. Surg. **95**: 302, 1932.
277. Lahey, F. H.: The Management of Goiter, J. Indiana M. A. **23**: 117, 1930.
278. Idem: Apathetic Thyroidism, Ann. Surg. **93**: 1026, 1931.
279. Masson, J. C., and Mueller, S. C.: Ovarian Tumors of Thyroid Tissue, Surg., Gynec. & Obst. **56**: 931, 1933.
280. Sanders, R. L.: Ovarian Thyroid, Am. J. Surg. **28**: 831, 1935.
281. Montgomery, M. L.: Lingual Thyroid: A Comprehensive Review, West. J. Surg. **43**: 661, 1935; **44**: 54, 122, 189, 1936.
282. Oswald, A.: Ueber das sogenannte gleichzeitige Vorkommen von Basedow und Myxödem beim gleichen Individuum, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **41**: 187, 1929.
283. Gley, E.: De l'exophthalmie consécutive à la thyroïdectomie. Presentation d'animaux, Compt. rend. Soc. de Biol. **1**: 858, 1910.
284. Friedgood, H. B.: Experimental Exophthalmos and Hyperthyroidism in Guinea Pigs. Clinical Course and Pathology, Bull. Johns Hopkins Hosp. **54**: 48, 1934.
285. Marine, D., and Rosen, S. H.: Exophthalmos of Graves's Disease. Its Experimental Production and Significance, Am. J. M. Sc. **188**: 565, 1934.
286. Justin-Besançon et al.: Recherches expérimentales sur l'exophthalmie de type basedowien, Bull. et mém. Soc. méd. d. hôp. de Paris **47**: 1883, 1931.
287. Labbe, M., et al.: Ètude sur la pathogenie des exophthalmies de type basedowien, Bull. et mém. Soc. méd. d. hôp. de Paris **42**: 1897, 1931.
288. Sainton, P., and Hesse, D.: La transformation d'un myxoedeme typique en goitre exophthalmique par la sommation thyroxi-adrenalinique, Bull. et mém. Soc. méd. d. hôp. de Paris **42**: 1856, 1931.

289. Reudemann, A. D.: The Ductless Glands as They Appertain to Eye Diseases and to Surgery, J. A. M. A. **97**: 1700, 1931.
290. Cattell, R. B.: Eye Complications in Exophthalmic Goiter, Ann. Surg. **100**: 284, 1934.
291. Plummer, W. A., and Wilder, R. M.: The Etiology of Exophthalmos, With Particular Reference to Exophthalmic Goiter, Arch. Ophthal. **13**: 833, 1935.
292. Zimmerman, L. M.: Exophthalmos Following Operation for the Relief of Hyperthyroidism, Am. J. M. Sc. **178**: 92, 1929.
293. King, B. T.: The Cause of Exophthalmos, West. J. Surg. **39**: 602, 1931.
294. Naffziger, H. C.: Progressive Exophthalmos Following Thyroidectomy; Its Pathology and Treatment, Ann. Surg. **94**: 582, 1931.
295. Sjostrom, P. M.: Studies of Postoperative Tetany, Acta chir. Scandinav. **68**: 325, 1931.
296. Ask-Upmark, E.: Thyrotoxicosis and Tetany. Some Aspects of the Mineral Metabolism in Morbus Basedowi, Endocrinology **16**: 369, 1932.
297. Boothby, W. M., Haines, S. F., and Pemberton, John deJ.: Postoperative Parathyroid Insufficiency, Am. J. Med. Sc. **181**: 81, 1931.
298. Stone, H. B., Owings, A. C., and Gey, G. O.: Transplantation of Living Grafts of Thyroid and Parathyroid Glands, Ann. Surg. **100**: 613, 1934.
299. Levine, M. M.: Sur le traitement de la tétanie après strumectomie à l'áide de la transplantation d'un os bouilli suivant la méthode d'Oppel, Lyón chir. **21**: 164, 1934.
300. Blumgart, H. L., and Yens, O. C.: Studies on the Velocity of Blood Flow. The Method Utilized, J. Clin. Investigation **4**: 1, 1927.
301. Blumgart, H. L., et al.: Studies on the Velocity of Blood Flow. The Circulatory Response to Thyrotoxicosis, J. Clin. Investigation **9**: 69, 1930.
302. Idem: The Circulation in Myxedema With a Comparison of the Velocity of Blood Flow in Myxedema and Thyrotoxicosis, J. Clin. Investigation **9**: 91, 1930.
303. Idem: The Velocity of Blood Flow and Other Aspects of the Circulation in Patients With Primary and Secondary Anemia and in Two Patients With Polycythemia Vera, J. Clin. Investigation **9**: 679, 1931.
304. Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease: The Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation, Medicine **10**: 1, 1931.
305. Blumgart, H. L., Levine, S. A., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris: The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathological Evidence of Thyroid Toxicity, Arch. Int. Med. **51**: 866, 1933.
306. Rosenblum, H. H., and Levine, S. A.: What Happens Eventually to Patients With Hyperthyroidism and Significant Heart Disease Following Subtotal Thyroidectomy? Am. J. Med. Sc. **185**: 219, 1933.
307. Blumgart, H. L., et al.: The Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathological States Without Clinical or Pathological Evidence of Thyroid Toxicity, Arch. Int. Med. **52**: 165, 1933.
308. Levine, S. A., et al.: Thyroidectomy in the Treatment of Advanced Congestive Heart Failure and Angina Pectoris, New England J. Med. **209**: 667, 1933.
309. Berlin, D. D.: Therapeutic Effect of Complete Thyroidectomy on Congestive Heart Failure and Angina Pectoris in Patients With No Clinical or Pathological Evidence of Thyroid Toxicity. II. Operative Technic, Am. J. Surg. **21**: 173, 1933.
310. Mixter, C. G., et al.: Total Ablation of the Thyroid for Angina Pectoris and Congestive Heart Failure, Ann. Surg. **100**: 570, 1934.
311. Brenner, O., et al.: Total Thyroidectomy in the Treatment of Congestive Heart Failure, Brit. M. J. **2**: 624, 1934.
312. Berlin, D. D., and Blumgart, H. L.: Treatment of Chronic Intractable Heart Disease by Total Thyroidectomy, New York State J. Med. **34**: 1047, 1934.
313. Blumgart, H. L., and Berlin, D. D.: The Importance of Decreased Cardiac Work in the Relief of Angina Pectoris by Total Ablation of the Thyroid, Am. J. Physiol. **109**: 11, 1934.

314. Blumgart, H. L., and Davis, D.: Hypothyroidism Induced by Complete Removal of the Normal Thyroid Gland in the Treatment of Chronic Heart Disease, Endocrinology **18**: 693, 1934.
315. Weinstein, A. A., et al.: The Mechanism of Early Relief of Pain in Cases With Angina Pectoris and Congestive Heart Failure After Total Ablation of the Normal Thyroid Gland, Am. J. Med. Sc. **187**: 753, 1934.
316. Berlin, D, D.: Total Thyroidectomy for Intractable Heart Disease: A Summary for Two and One-Half Years' Surgical Experience, J. A. M. A. **105**: 1104, 1935.
317. Ochsner, A., and Gillespie, C.: Total Thyroidectomy for Cardiac Disease, New Orleans M. & S. J. **88**: 422, 1936.
318. Clark, R. J., et al.: Total Thyroidectomy for Heart Disease, New England J. Med. **214**: 277, 1936.
319. Barach, A. L., et al.: Oxygen Treatment and Thyroid Ablation in the Treatment of Heart Disease, Ann. Int. Med. **9**: 1513, 1936.
320. Parsons, W. H., and Purks, W. K.: Total Thyroidectomy for Heart Disease, Ann. Surg. **105**: 722, 1937.
321. Hertzler, A. E.: Evaluating the Results of Total Thyroidectomies in Cardiac Disease, Am. J. Surg. **29**: 342, 1935.
322. Levine, S. A., and Eppinger, E. C.: Further Experiences With Total Thyroidectomy in the Treatment of Intractable Heart Disease, Am. Heart J. **10**: 736, 1935.
323. Thompson, W. O., et al.: The Iodine in the Thyroid Gland, West. J. Surg. **41**: 431, 1933.
324. Means, J. H., and Lerman, J.: The Symptomatology of Myxedema: Its Relation to Metabolic Levels, Time Intervals and Rations of Thyroid, Arch. Int. Med. **55**: 1, 1935.
325. De Wesselow, O. L. V.: Myxoedema, Practitioner **135**: 757, 1935.
326. Kena-Apajalahti, L.: Studien über Myxoedem bei Kindern, Acta Soc. med. fenn. duodecim. **19**: Fasc. 1, No. 2, 1934.
327. Soiland, A., et al.: Radiotherapy in Thyroidism, Am. J. Surg. **9**: 123, 1930.
328. Goodwin, G. M., and Smith, M. K.: Results of Treatment of Toxic Goiter From Standpoint of Basal Metabolic Rate, New York State J. Med. **31**: 627, 1931.
329. Hayer, E.: Unserer Erfahrungen mit den Röntgenbehandlung der Thyreotoxikosen, Klin. Wchnschr. **10**: 297, 1931.
330. Engel, A.: Die Behandlung von Morbus Basedowii, Acta med. Scandinav. **79**: 125, 1932.
331. Quigley, D. T.: The Radium Treatment of Toxic Types of Goiter, Radiology **18**: 576, 1932.
332. Parcelier: Indications operatoires et valeur therapeutique du traitement chirurgical dans la maladie de Basedow, J. de méd. de Bordeaux **109**: 607, 1932.
333. Williams, A. H.: X-ray Treatment in Goiter Illness, With Results Reported and Comments Made on 200 Individually Controlled Cases, Radiology **18**: 553, 1932.
334. Menville, L. J.: The Radiological Aspect of Thyrotoxicosis, Radiology **18**: 568, 1932.
335. Lüdin, M.: Zur Strahlentherapie der Basedow'schen Krankheit, Acta radiol. **19**: 28, 1933.
336. Dunhill, Sir P.: Thyrotoxicosis: Its Surgical Aspects, Brit. M. J. **2**: 1034, 1935.
337. Gallino, M. M.: Roentgenterapia del hypertiroidismo, Semana méd. **41**: 345, 1934.
338. Allison, O. W.: Radium Treatment of Toxic and Exophthalmic Goiter, Illinois M. J. **55**: 133, 1929.
339. Gerber, I.: Radiation Treatment of Toxic Goiter, New England J. Med. **204**: 95, 1931.
340. Schteingart, M.: Les goitres adénomateux, Rev. sud-am. de méd. et de chir. **1**: 1193, 1930.
341. Zweifel, C.: Gibt es Todesfälle im Anschluss an Basedowbestrahlung? Acta radiol. **14**: 33, 1933.
342. Seed, L.: The Determination of Operability in Exophthalmic Goiter, West. J. Surg. **40**: 613, 1932.
343. Starr, P., and Patton, H.: Observations of Remission in Hyperthyroidism Induced by Pregnancy Urine Extracts, Ann. Int. Med. **88**: 25, 1935.

344. Pemberton, John deJ.: Recurring Exophthalmic Goiter. Relation to Amount of Tissue Preserved in Operation, Tr. South. S. A. **42**: 147, 1930.
345. Jackson, Arnold S.: The Prevention of Persistent and Recurrent Hyperthyroidism, Surg., Gynec. & Obst. **58**: 590, 1934.
346. Richter, H. M.: The Surgical Treatment of Thyrotoxicosis, Radiology **18**: 542, 1932.
347. Thompson, W. O., et al.: The Relation Between the Preoperative Condition of the Patient and the Operative Mortality in Exophthalmic Goiter, Illinois M. J. **67**: 53, 1935.
348. Horsley, G. W.: Surgical Treatment of 183 Consecutive Thyroid Cases With No Mortality, Virgina M. Monthly **62**: 249, 1935.
349. Drennen, Earle: An Analysis of 300 Consecutive Thyroidectomies, Ann. Surg. **106**: 717, 1937.
350. Goetsch, E.: Mortality in Goiter Operations, Ann. Surg. **94**: 167, 1931.
351. Maes, U., Boyce, F. F., and McFetridge, E. M.: Hyperthyroidism in the Negro With an Analysis of 73 Cases, West. J. Surg. **42**: 456, 1934.
352. Rogers, J.: Therapeutic Failures After Operation for Hyperthyroidism, Ann. Surg. **93**: 1031, 1931.
353. Elkin, Daniel C.: Thyroidectomy: Factors Influencing the Mortality, South. M. J. **30**: 260, 1937.
354. Noehren, A. H.: The Results of Thyroidectomy, Ann. Surg. **93**: 1045, 1931.
355. Coller, F. A., and Potter, E. B.: The End-Results of Thyroidectomy, Ann. Surg. **94**: 568, 1931.
356. Wallace, H. L., and Wevill, L. B.: Toxic Goiter and Analysis of the Results of Surgical Treatment, Edinburgh Med. J. **40**: 598, 1933.
357. Pemberton, John deJ.: Surgery of Substernal and Intrathoracic Goiter, Arch. Surg. **2**: 1, 1921.
358. Lahey, F. H.: The Surgical Management of Intrathoracic Goiter, Surg., Gynec. & Obst. **53**: 346, 1931.
359. Clairmont, P.: Ueber die Struma endothoracica, München. med. Wchnschr. **80**: 643, 1933.
360. Waterworth, S. J.: Preoperative and Postoperative Treatment of Bad Risk +4 Toxic Goiter, West. J. Surg. **41**: 531, 1933.
361. Shaw, R. C.: Cervical Sympathetic and Its Relation to Thyroid Gland, Brit. M. J. **1**: 495, 1929.
362. Marine, D.: Disease of the Thyroid and Parathyroid Glands, Tice's Practice of Medicine **8**: 197, Hagerstown, Md., 1930, W. F. Prior Company, Inc.
363. Idem.: The Physiology and Principle Interrelation of the Thyroid, J. A. M. A. **104**: 2250, 1935.
364. Idem.: The Pathogenesis and Prevention of Simple or Endemic Goiter, J. A. M. A. **104**: 2334, 1935.
365. Zimmerman, L. M.: Thyroid Literature of 1932, Internat. Abstr. Surg., p. 193, Sept., 1933.
366. Starr, Paul: A Commentary on Some of the 1935 Literature on Thyroid Disease, Internat. Abstr. Surg., p. 313, Oct., 1936.
367. Crile, George W., and others: Diagnosis and Treatment of Diseases of the Thyroid Gland, Philadelphia and London, 1932, W. B. Saunders Company.
368. Eberts, E. M., Fitzgerald, R. R., and Silver, P. G.: Surgical Diseases of the Thyroid Gland, Philadelphia, 1929, Lea & Febiger.
369. Sloan, E. P.: The Thyroid, Springfield, Ill., 1936, Charles C. Thomas, Publisher.
370. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, 1937, J. B. Lippincott Company.

Review of Recent Meetings

REVIEW OF THE SIXTH ANNUAL MEETING OF THE HARVEY CUSHING SOCIETY, PHILADELPHIA, MAY 6, 7, AND 8

JAMES C. WHITE, M.D., BOSTON, MASS.
(From the Massachusetts General Hospital)

THE sixth annual meeting of the Harvey Cushing Society was held at Philadelphia May 6, 7, and 8. Out of a series of over thirty papers which were presented by members of the Society and invited guests, the following have been abstracted:

Dr. John Fulton discussed the rôle of the cerebral cortex in the regulation of blood pressure. Very light ether anesthesia is most suitable for these experiments and the animal must be curarized to eliminate somatic motor responses. Under these circumstances Fulton was able to map out a rich representation of vasoconstrictor as well as vasodilator points in the cortex. These tend to overlap the somatic areas, i.e., autonomic representation is found only in those areas (motor and premotor) from which somatic movements are obtained in the uncurarized preparation. This arrangement doubtless enables somatic motor activity to be accompanied by appropriate autonomic adjustments. The vasodilator effect is brought out by splanchnicectomy, and the vasoconstrictor response by cutting the vagi (**E. C. Hoff** and **Green**). Barbiturates destroy these reactions, although they leave the somatic reactions of Area 4 intact. There are striking species differences in cortical representation of autonomic activity; e.g., in the dog there is contralateral vasodilation after removal of the frontal area, whereas, in macaques there is vasoconstriction.

Dr. Franklin Jelsma reported two cases of Schüller-Christian's disease. This condition is a form of lipoid dystrophy in which xanthomatous deposits occur in the cranium and flat bones principally, occasionally in the long bones. According to the location of the deposits, certain symptoms will present. Pressure of the lipoid material upon the region of the tuber cinereum may cause a diabetes insipidus; likewise exophthalmus may be present if the lipoid material is in sufficient quantity in the retrobulbar region.

The disease is one of disturbed lipoid metabolism with general systemic effects as well as the local effects caused by the lipoid deposits. It may be grouped with the series of lipodystrophies which includes Gaucher's disease, Niemann-Pick's disease, and possibly Tay-Sach's disease. One of the cases reported was unusual in that the diabetes insipidus improved completely with roentgen therapy. In this case the blood cholesterol was 346 mm. per 100 c.c. of blood. Low fat diet and roentgen therapy seemed to offer the best results.

Dr. J. G. Lyerly reported two unusual instances of meningiomas situated posteriorly in the lateral ventricles. These apparently arose from the choroid plexus, which brings in some pia-arachnoid in its development. Ventriculograms in Lyerly's patients showed no hydrocephalus, and **Bucy** cited a case with similar findings, but **Fincher** and **Spurling** reported three cases in which there was extensive enlargement of the ventricle which was blocked by the tumor.

Received for publication, June 17, 1937.

Dr. Frederick Schreiber pointed out the dangers to the central nervous system of the increasing use of heavy sedation to promote painless labor. He has studied the birth history of twenty cases given multiple heavy doses of scopolamine or barbiturates in which the outlook for spontaneous delivery was good, but the child was born with cerebral damage.

The type of drug is not as important as the anoxemia induced. Such babies are born blue. They are hard to resuscitate and some die. Both mothers and babies may develop evidence of cerebral injury. The babies may show spastic paralysis and severe cortical atrophy on encephalography. Secondary to these organic changes, mental deterioration and epilepsy may result. Some of the mothers have shown mental changes. They become jittery and cry easily. Occasionally the evidence of injury to the higher cerebral functions has been definitely increased by multiple deliveries under heavy sedation with an accompanying high grade of anoxemia.

The incidence of surgical interference in the normal course of labor has risen with the use of analgesia. Rapid mechanical molding of the head with forceps or version reproduces the dangers of precipitate delivery. A blue baby, born of a drugged mother, is potentially a spastic, an epileptic, or an idiot.

Dr. Tracy J. Putnam and **Dr. Donald Munro** presented reports of three patients who had an unusual postoperative reaction to high anterolateral or anterior cordotomies. All of these were in good condition immediately after operation, but subsequently developed profound mental changes (confusion, delirium, and hallucinations) leading to death within a week or two. High cord tumors and cervical fractures have caused a similar condition. This progressive confusional syndrome is probably due to anoxemia of the brain. The oxygen content of the arterial blood drops to 12 or 13 per cent in some cases, close to levels where symptoms are known to develop. In others, sluggish circulation and anemia add to the disturbance. The picture resembles mountain sickness or decompensation, and is most common in older people. Anemia and sedatives increase it. The treatment recommended is transfusion and the use of a respirator as indicated. Anesthetics, sedatives such as morphine and the barbiturates, and carbon dioxide inhalations should be avoided.

Dr. W. McK. Craig presented nine cases of intracerebral hemorrhage in which operation had been carried out. In reviewing the literature, he stated that Dr. Cushing was probably the first surgeon to operate for subcortical hemorrhage. It was interesting to note that trauma played a definite rôle in two of the nine cases, was suggested in a third, was suspected in a fourth, and in a fifth a subcortical hemorrhage was found twelve years after an injury to the head. In two other cases, the cerebral hemorrhages followed emotional stress, and in one case the hemorrhage was associated with rheumatic heart disease and endocarditis.

Craig further stated that intracerebral hemorrhages have been attributed to faulty structure of the arterioles or venules within the substance of the brain, with subsequent rupture of small sacculations. In view of the fact that the hemorrhages did not result in extensive extravasation, he suggested that they were of venous rather than arterial origin. A history of trauma was always suggestive of hemorrhage and yet in the cases in which encephalograms or ventriculograms were made, they did not reveal shadows or defects characteristic of hemorrhage. A diagnosis of subcortical hemorrhage was established at the time of operation, and craniotomy and incision of the cortex, drainage, and removal of the residual clots was the treatment carried out in all cases. A census of the Society yielded twenty-seven such cases.

The symptoms in all cases consisted of those of an expanding intracranial lesion. Headache, choked discs, convulsions, and hemiparesis were prominent clinical manifestations of intracerebral hemorrhage.

REVIEW OF THE THIRTY-EIGHTH ANNUAL MEETING OF THE AMERICAN PROCTOLOGIC SOCIETY

CURTICE ROSSER, M.D., DALLAS, TEX.

(From the Division of Proctology, Baylor University Department of Medicine)

THE American Proctologic Society, organized in 1899 by the then outstanding proctologists of this country, has had uninterrupted yearly programs since that time. The Society's Fellowship list is limited to seventy-five, there being seven Honorary Fellows from Europe and France and several Associates from Canada and Cuba. The session in June of this year was held in Atlantic City under the presidency of **Marion C. Pruitt,** of Atlanta, who was succeeded by **Harry Z. Hibshman,** of Philadelphia.

The emphasized program features were two extended symposiums on anesthesia and colorectal malignancy, and the appearance in papers or discussions of several nonproctologists, including gastroenterologists (**Crohn,** of New York; **Mackie,** of New York), a pathologist (**Lawrence Weld Smith,** of Philadelphia) and a regional anesthetist (**Lundy,** of Rochester, Minn.).

Burrell Crohn presented his findings in connections with what he believes to be three separate entities, ileitis, right-sided colitis, and ordinary chronic ulcerative colitis which is a process beginning low in the left colon and extending upward. Both ileitis and right-sided colitis occur in young individuals, the average age of the patients being twenty-four years. **Daniel Jones,** of Boston, is under the impression that ileocolitis is chiefly a disease of the Jewish race, although Crohn doubts this because of reports of numerous cases from various parts of Europe; Crohn believes right-sided colitis to be nonspecific, usually beginning in the hepatic flexure or ascending colon with slow progressive advance in both directions. Although the prognosis under medical treatment is poor, the disease is much more amenable to surgical treatment than typical left colitis, providing extirpation of the diseased gut be carried out radically. **Berg,** of New York (reported by Crohn), after attempting segmental resection with fair results, now resects the entire colon to the sigmoid in three stages. In fifteen cases, one patient died in five weeks, two patients died considerably later; the twelve who survived are apparently cured.

The beneficial although perhaps temporary effects of long-continued cod liver oil instillations in chronic ulcerative colitis which were reported by **Best,** of Omaha, were corroborated by **Rose Spiegel,** working simultaneously in New York.

Various reports on neoplasms suggested that in some circumstances the accurate diagnosis of adenocarcinoma of the rectum may be clouded by the presence of benign intrarectal or pelvic infiltrating tumors (**Daniels,** of Los Angeles) such as endometriosis (**Schofield** and **Bacon,** of Philadelphia), neurofibroma (**Keith,** of Hartford), tuberculosis (**Wheeler,** Indianapolis), adenomas (**Martin,** Louisville, and **Scarborough,** San Francisco), and diverticulum (**Freund,** New York City); or by infiltration of the bowel by extrarectal malignancy such as ovarian carcinoma (**Kleckner,** of Allentown) or sarcoma (**Werner,** Philadelphia).

The therapy of rectal cancer is apparently not yet so standardized that discussion is unnecessary. In the symposium on cancer, the value of radon implants

Received for publication, June 24, 1937.

and local removal in those unsuitable for surgery was mentioned by **Binkley** of New York; desiccation was advocated in suitable cases by **E. G. Martin**, of Detroit and **Buie** of Rochester, Minn., while **Lynch** and **Hamilton**, of New York City, while advocating radical surgery, had a kind word to say for the perineal anus.

The majority of those answering **Cartwright's** questionnaire (Fort Wayne) favored radical rather than temporizing measures in strangulated hemorrhoids. **Yeomans**, of New York City, discussed the anatomic relations and repair of an infrequent type of hernia through the levator ani muscle, and **Hibshman**, of Philadelphia, advocated wide and early drainage of supralevator abscesses through the posterior ischiorectal space.

Woolf, of San Francisco, reflected what I believe to be the majority opinion of American proctologists when insisted that proctology is a surgical specialty and that it is essential that those entering the field have surgical training that includes the abdominal zone.

The transactions of the Society are published in a single annual volume.

REVIEW OF THE MEETING OF THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS

MORTON F. MASON, PH.D., NASHVILLE, TENN.
(From the Department of Biochemistry, Vanderbilt University)

THE Effect of Epinephrine Injected Intravenously at a Constant Rate in Normal and Hypertensive Cases, Alfred E. Koehler, Norman Marsh, and Elsie Hill (Santa Barbara Cottage Hospital and the Sansum Clinic, Santa Barbara).—Epinephrine 1:50,000 was administered intravenously in patients at a constant rate of 2 mg. per hour. In normal patients there was a constant sustained rise of systolic blood pressure. The diastolic pressure also rose at first, but later tended to drop below the control period. The basal rate increased about 30 per cent and there were increases in blood sugar and lactic acid. Almost immediately after cessation of injection, both systolic and diastolic pressures dropped markedly below their values during the control period. In patients with essential hypertension, the lactic acid increase was not as great. The average blood pressure rise was consistently greater than in the case of normal patients and the drop and duration of drop of blood pressure after cessation of injection were greatly increased. There was no evidence that myocardial failure was related to the drop in pressures following injection.

The Prolongation of Insulin Action, A. M. Fisher and D. A. Scott (Connaught Laboratories, University of Toronto).—Incubated preparations containing spermine, zinc, and insulin produce prolonged hypoglycemia in rabbits and dogs. A preparation from beef blood has also been found to modify (prolong) ordinary insulin action. Zinc is an essential constituent of the various modified insulin preparations.

Some Observations on the Source of Urinary Cystine in Cystinuria, E. Brand, R. J. Bloch, and G. F. Cahill (Department of Chemistry, New York Psychiatric Institute and Hospital, and Squier Urological Clinic, Presbyterian Hospital, New York).—Observations on the metabolism of casein and lactalbumin in a case of cystinuria further support the hypothesis that the urinary cystine in patients with this error of metabolism is derived, not from cystine of dietary protein, but from methionine.

A Volumetric Method for the Determination of Acacia in Serum, Lymph, and Urine, Marschelle H. Power (Division of Biochemistry, the Mayo Foundation, Rochester, Minn.).—A method was described permitting the accurate determination of acacia in serum, lymph, and urine. The acacia is precipitated from trichloracetic acid filtrates of serum or lymph, or from urine by treatment with acetone. The precipitated acacia is oxidized with chromic acid and the excess chromic acid estimated iodometrically. For details of the method, the original paper should be consulted.

Quantitative Determination of Prothrombin, Armand J. Quick and Madeline Leu (Department of Pharmacology, Marquette University School of Medicine, Milwaukee).—The rate of coagulation is assumed to be a function of the concentration of thrombin which in turn is proportional to the concentration of prothrombin when an excess of thromboplastic substance is present with ade-

Received for publication, May 17, 1937.

quate calcium ions. The determination is performed as follows: 9 vol. of blood mixed with 1 vol. of 0.1 M sodium oxalate are centrifuged and the plasma separated. A small test tube containing 0.1 c.c. of the plasma mixed with 0.1 c.c. of thromboplastic substance (an emulsion prepared from rabbit brain) is kept at 40° in a water-bath; 0.1 c.c. of 0.025 M calcium chloride is quickly added and the time required for clotting noted. The times are quite constant for normal animals of the same species, but there are species differences. The actual observed time varies somewhat with different thromboplastin preparations.

Fatty Livers in Geese, Produced by Overfeeding, Eunice Flock, Jesse L. Bollman, H. R. Hester, and Frank C. Mann (Division of Experimental Medicine, the Mayo Foundation, Rochester, Minn.).—Fatty livers were produced in geese by continued overfeeding with a high carbohydrate diet during the day. These livers contained up to 15 per cent fatty acids. When night feeding was also employed, values as high as 48 per cent were found. This fat was more saturated than depot fat. The water content of the livers diminished with increasing fat content, but the glycogen contents varied. Large increases in depot fat were observed.

Further Observations of the Effect of Parenteral Injection of Amino Acids and Related Substances Upon Creatine Formation and Storage in Rats, H. H. Beard, T. S. Boggess, and P. Pizzolato (Department of Biochemistry, Louisiana State University Medical Center, New Orleans).—A large number of dietary experiments on rats support the contention that urea and glycine as such, or arising as intermediaries in amino acid metabolism, are the precursors of creatine.

The Dietary Production of Parathyroid Hypertrophy in Rabbits, E. J. Baumann and D. B. Sprinson (Laboratory Division, Montefiore Hospital, New York).—Rabbits fed on a diet of carrots and oats develop parathyroid hypertrophy, the gland weights increasing as much as 400 per cent. The Ca:P ratio of this diet is 0.5 in contrast to a ratio of 4 in the stock diet. The serum calcium remains normal, the inorganic phosphate is somewhat depressed, and an increase in circulating parathormone is demonstrable (Hamilton's test). In adult rabbits the serum phosphatase content is markedly depressed.

The Effect of Vitamin B_1 on the Respiratory Quotient, Dorothy V. Whipple and Charles F. Church (Department of Pediatrics, School of Medicine, University of Pennsylvania, Philadelphia).—When vitamin B_1 deficient rats were given glucose subcutaneously, the respiratory quotient remained below 1, while those of isocaloric controls receiving the vitamin were above unity. Crystalline vitamin B_1 raised the respiratory quotients of animals with severe beriberi symptoms to values also above unity. The observations were in harmony with the authors' hypothesis that vitamin B_1 must be present in the metabolic mixture to permit synthesis of fat from carbohydrate in the animal body.

The Toxicity of Calciferol for Rabbits, Arthur M. Hartman (Division of Nutrition and Physiology, Bureau of Dairy Industry, United States Department of Agriculture, Beltsville).—Young rabbits placed on diet of natural foods were administered calciferol by mouth in various doses six days per week. The calciferol was dissolved in cottonseed oil. When the diet contained alfalfa of good quality, the toxicity of the calciferol was not in evidence at as low levels of dosage as when a poor quality of alfalfa was used. The toxic effects were observed more frequently in males than in females. Autopsies disclosed degenerative changes including metastatic calcification in the aorta and kidneys of these animals on dosages of calciferol as small as 0.02 mg. per day. In experiments prolonged over several months dosages not immediately toxic produced these changes. The calciferol was pure according to spectrophotometric tests.

Physiologic Effects of Phenol-Contaminated Drinking Waters, V. G. Heller and Lee Pursell (Oklahoma Agricultural Experiment Station, Stillwater).—The toxicity of long-continued consumption by rats of water containing phenol was investigated. A water supply containing as much as 0.8 per cent phenol does not interfere with growth reproduction and lactation. Involved nutritional studies indicate that normal metabolism is not disturbed until the contamination of water with phenol approaches one per cent. The phenol is readily detoxified and the conjugated compounds appear in the urine.

The Effects of Minute Amounts of Lead on the Animal Organism, M. K. Horwitt and George R. Cowgill (Laboratory of Physiological Chemistry, Yale University School of Medicine, New Haven).—The point of view that small amounts of lead in the diet are deleterious was subjected to experimental test using rats. Growth was not affected when diets containing up to 100 mg. per kilogram of lead were fed. No anemia developed nor was "stippling" observed. In three successive generations reproduction was normal. Many experimental diets in common use in various laboratories were found to contain more than the present government tolerance of 2.6 mg. lead per kilogram, none of these diets having any untoward effects on the animals receiving them. The dithizone micromethod was employed in determining lead.

REVIEW OF THE MEETING OF THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

MORTON F. MASON, PH.D., NASHVILLE, TENN.
(From the Department of Biochemistry, Vanderbilt University)

ABSTRACTS OF PAPERS PRESENTED*

Correlation of Serum Iron, Bone Marrow, and Blood Cell Changes Following Specific Therapy in the Macrocytic Anemias

Carl V. Moore (by invitation) **and Charles A. Doan, Ohio State University**

The observation has been made that the nonhemoglobinous iron of the serum is higher than normal in the relapse phase of pernicious anemia. Beginning within twenty-four hours after the institution of adequate liver therapy, this iron fraction of the blood falls precipitously to a level that is below the normal range. The change thus precedes by three or four days the reticulocytosis that follows therapy.

Consequently, in order that the reequilibration in the serum iron could be more adequately understood with reference to the altered physiology of the erythropoietic tissue, serial supravital differential cell counts of sternal marrow, obtained by the puncture technique, were made for two patients with pernicious anemia both before and after the commencement of specific therapy. Blood for an analysis as to iron content was drawn within a few minutes after the sternal puncture was made.

Within twenty-four hours after the administration of liver began, there was evident in the bone marrow a definite shift to the right in the level of the erythrocytic maturation. Megaloblasts were fewer, and mitotic figures were markedly increased. During the subsequent forty-eight hours a transition from a predominantly erythroblastic to a predominantly normoblastic marrow, with resultant discharge of reticulated red cells into the peripheral blood, was accomplished. The fall in serum iron closely paralleled the cytologic changes, reaching its greatest depression at the time of maximum delivery of erythrocytes from the bone marrow (the reticulocyte peak in the peripheral blood). These findings are interpreted as offering further evidence for the concept of serum iron as iron in transportation. It is considered that the decrease in serum iron occurred and persisted during these experiments for two reasons: (1) After the institution of liver therapy any increase in hemolytic activity promptly subsided; and (2) with the increase in synthesis of hemoglobin coincident with the reinstitution of normal maturation, the iron being transported in the serum was withdrawn from the blood by the bone marrow and utilized at a more rapid rate than normal. The low serum iron under these conditions does not reflect inadequate storage of iron in the body depots.

In addition to hemoglobin iron and serum iron, a third form of blood iron has been described: "easily split-off iron." It is possibly, but not as yet certainly, of nonhemoglobinous origin. This third fraction remained at a fairly constant level during the changes described.

One of the two patients studied had Addisonian pernicious anemia; the other had pernicious anemia of pregnancy, in which the disease had been produced primarily by a deficiency in a dietary extrinsic factor. The responses in cytologic and serum iron in the two patients were identical and constitute further evidence

Received for publication, May 17, 1937.
*Authors' abstracts.

that, from the standpoint of pathologic physiology, Addisonian pernicious anemia and pernicious anemia of pregnancy reflect disturbances in essentially identical mechanisms.

Chronic Hepatogenic Hypoglycemia Due to Ascending Cholangiolitis, With Recovery Following Cholecystectomy

Jerome W. Conn (introduced by Raphael Isaacs), **University of Michigan Medical School**

The literature reveals no report of a case of chronic hepatogenic hypoglycemia due to ascending infectious hepatitis. An extensive study of the metabolism in such a case was made before and after the removal of the source of the ascending hepatitis. A remarkable recovery of the previously impaired glycogenic function of the liver was observed.

Before cholecystectomy, frequent episodes of coma occurred spontaneously, with the blood sugar at such times ranging between 14 and 20 mg. per hundred cubic centimeters. Dextrose tolerance tests suggested that the hypoglycemia was due to deficient hepatic glycogenesis rather than to excessive production of endogenous insulin. Indirect calorimetry showed that while the blood sugar was dropping to hypoglycemic levels the oxidation of dextrose was normal. Numerous types of tests consistently revealed deficient hepatic function.

Exploratory laparotomy revealed a grossly normal pancreas. Biopsy of the liver showed active chronic cholangiolitis and biliary cirrhosis.

After cholecystectomy, gradual improvement occurred until virtual recovery was attained. No spontaneous hypoglycemic attack has occurred since operation. Dextrose tolerance tests are essentially normal. All tests show normal hepatic function. Indirect calorimetry still reveals normal oxidation of dextrose.

This study indicates that chronic infection of the biliary tract may so injure the glycogenic and glycogenolytic functions of the liver that severe spontaneous hypoglycemia results.

Parenteral Protein in Pneumonias

Clyde Brooks, Louisiana State University Medical Center, New Orleans

In 1,200 cases of pneumonia, including all forms and patients of all ages, the best routine treatment of the medical center was used, including a hygienic regimen, nursing, medication, and surgical intervention when indicated.

One half of the patients were used as controls; the other half were treated by the parenteral administration of deuteroproteose.

The results show that among the controls the death rate was 39 per cent for lobar pneumonia and 32 per cent for bronchopneumonia. The death rate in the cases in which treatment was by deuteroproteose was 10 per cent for lobar pneumonia and 9 per cent for bronchopneumonia.

The results are encouraging, if not conclusive. They indicate that the parenteral use of deuteroproteose reduces the death rates for both lobar and bronchial pneumonia.

Effect of Artificial Fever on Experimental Rabies

F. D. McCrea (introduced by Douglas H. Sprunt) **and Harold M. Horack** (introduced by Douglas H. Sprunt), **Duke University**

Rabbits were inoculated intracerebrally with fixed rabies virus. Then, by exposure of the animals to radiant heat, their body temperatures were elevated and maintained between 41.2° and 41.8° C. (106.1° and 107.2° F.). Unheated controls were checked against each heated group.

The experimental animals were divided into five groups according to the number of hours of exposure to heat and the time of exposure as follows: (1) seven or twelve hours the day of inoculation; (2) six, seven, or twelve hours twenty-four hours after inoculation; (3) seven hours the same day and seven hours forty-eight hours after inoculation; (4) twelve hours the same day and twelve hours forty-eight hours after inoculation; (5) twelve hours the same day and twelve hours forty-eight hours after inoculation.

The first four groups received 0.2 c.c. of virus diluted 1:200; the fifth group, 0.2 c.c. of virus diluted 1:100.

All controls and heated animals in groups 1, 2, and 3 died of rabies within from seven to fourteen days. In group 4, all nine controls died of rabies; of the fifteen heated animals, three died during the heating period and five of causes other than rabies; seven survived and by February 13, 1937, had outlived their corresponding controls sixty-two, seventy-six, ninety, one hundred and two and two hundred and twenty days. Two controls and four heated animals comprising group 5 died of rabies. Whether this is significant we do not know.

Forty white rats were inoculated intracerebrally with 0.05 c.c. of virus diluted 1:50 and on up to 1:400. In all the rats symptoms typical of rabies developed, followed by death. Blood serum from two surviving rabbits was mixed with virus, making dilutions of the latter varying from 1:50 to 1:400; these were incubated two hours at 37.5° C. and inoculated intracerebrally into thirty-six rats. All died with symptoms typical of rabies. Like dilutions were inoculated intracerebrally into eight rabbits, which also died with paralyses typical of rabies. Serum from surviving rabbits apparently has no protective action and seems to transfer no immunity.

Values of Phosphatase in the Serum and Bile of Dogs With Experimental Biliary Fistulas and in Dogs With Complete Biliary Obstruction

Siegfried Thannhauser (by invitation), **Stephen Maddock, M. Reichel** (by invitation), **and Jerome F. Grattan** (by invitation),
Boston City Hospital

Experience with increasing and decreasing phosphatase activity and with the splitting of sphingomyelins by phosphatase suggested the possibility of activating the phosphatase of the blood serum in vitro. It was found that cevitamic acid (introduced as ascorbic acid) in appropriate concentrations would activate serum phosphatase. The activation is proportional to the concentration of cevitamic acid within certain limits and bears no relation to time. The optimum pH is identical with that of normal phosphatase activity. As it was known that following complete biliary obstruction a marked rise in serum phosphatase occurred, the common bile duct was ligated in series of dogs, and studies were made of the serum phosphatase. It was found that after ligation the phosphatase of these serums rose from about 2 to about 100 Bodansky units in three weeks. These same serums were activated with 5 mg. of cevitamic acid per tenth cubic centimeter. The activity of all the serums rose to about 150 Bodansky units regardless of the initial value prior to activation, so that an almost uniform maximum activity was found after the addition of cevitamic acid, which was independent of the progressive increase in the concentration of phosphatase produced by biliary obstruction.

Dogs with total biliary fistulas were also studied, and it was found that the serum phosphatase rose to about ten times the normal levels. Cevitamic acid was effective in the serums of these dogs in the same manner as already described. The values of the phosphatase in the bile coming from the fistulas showed, in contrast to the values for that in the serum, almost complete activation.

In cats it was found that ligation of the common bile duct does not cause an appreciable rise in the blood phosphatase, but that the serums of these animals can be activated by cevitamic acid in the same manner as the serums of the dogs or human serums.

These experiments indicate that in complete biliary obstruction in the dog the increase in the value for circulating phosphatase is due to an increase in the activity of the phosphatase and not to an increase in its amount. They also indicate that in dogs with experimental biliary fistulas an increase in circulating phosphatase occurs without obstructive jaundice. It seems that the diagnostic value of an increase in serum phosphatase in certain pathologic conditions is limited.

Book Review

Medical Urology. By Irvin S. Koll. Pp. 431, with 92 text illustrations and 6 color plates. St. Louis, 1937, The C. V. Mosby Company. $5.

The author has prepared this volume . . . "to present the subject in such a manner as to be of practical value to the general physician and an aid to the medical student." He adheres closely to this purpose throughout and has succeeded in presenting a very good synopsis of urologic principles. The book is profusely illustrated. Where there is indication for further study of the material in any chapter, extensive bibliographical references are appended.

Gonorrhea and its complications are discussed with a view to establishing a conservative, though adequate, system of treatment. In these chapters the author has been particularly careful in stating the reasons underlying the methods which are suggested, so that the practitioner or student can proceed to their application in a rational manner. That part of the book which is devoted to consideration of the major surgical problems in urology contains few details of treatment. There is no pretense at description of operations. Cystoscopy is considered principally from the standpoint of its diagnostic value. In the chapter on the surgical diseases of the prostate, the author has wisely confined his remarks to the principles of diagnosis and preoperative care. The reader is neither subjected to a technical description of the different methods for surgical attack on the prostate nor is he drawn into controversy regarding the relative merits of prostatectomy and transurethral resection.

This book can be only of passing interest to the specialist in urology, but it provides both the general physician and the medical student with a useful practical handbook for guidance.